

SUBSTITUTED ARYLAMINE DERIVATIVES AND METHODS OF USE

This application is a continuation of U.S. Patent Application 10/197,960 filed July 17, 2002 which is a continuation-in-part of U.S. Patent Application 10/046,526 filed January 10, 2002 claiming the benefit of U.S. Provisional Application Nos. 60/261,360, filed January 12, 2001, and 60/323,686 filed September 19, 2001, which are hereby incorporated by reference.

FIELD OF THE INVENTION

This invention is in the field of pharmaceutical agents and specifically relates to compounds, compositions, uses and methods for treating cancer and angiogenesis-related disorders.

BACKGROUND OF THE INVENTION

Protein kinases represent a large family of proteins which play a central role in the regulation of a wide variety of cellular processes, maintaining control over cellular function. A partial list of such kinases includes abl, Akt, bcr-abl, Blk, Brk, Btk, c-kit, c-met, c-src, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDK10, cRaf1, CSF1R, CSK, EGFR, ErbB2, ErbB3, ErbB4, Erk, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, flt-1, Fps, Frk, Fyn, Hck, IGF-1R, INS-R, Jak, KDR, Lck, Lyn, MEK, p38, PDGFR, PIK, PKC, PYK2, ros, tie, tie2, TRK, Yes, and Zap70. Inhibition of such kinases has become an important therapeutic target.

Certain diseases are known to be associated with deregulated angiogenesis, for example ocular neovascularisation, such as retinopathies (including diabetic retinopathy), age-related macular degeneration, psoriasis, hemangioblastoma, hemangioma, arteriosclerosis,

inflammatory disease, such as a rheumatoid or rheumatic inflammatory disease, especially arthritis (including rheumatoid arthritis), or other chronic inflammatory disorders, such as chronic asthma, arterial or post-transplantational atherosclerosis, endometriosis, and neoplastic diseases, for example so-called solid tumors and liquid tumors (such as leukemias).

At the center of the network regulating the growth and differentiation of the vascular system and its components, both during embryonic development and normal growth, and in a wide number of pathological anomalies and diseases, lies the angiogenic factor known as Vascular Endothelial Growth Factor" (VEGF; originally termed 'Vascular Permeability Factor', VPF), along with its cellular receptors (see G. Breier et al., Trends in Cell Biology, 6:454-456 (1996)).

VEGF is a dimeric, disulfide-linked 46-kDa glycoprotein related to "Platelet-Derived Growth Factor" (PDGF); it is produced by normal cell lines and tumor cell lines; is an endothelial cell-specific mitogen; shows angiogenic activity in *in vivo* test systems (e.g. rabbit cornea); is chemotactic for endothelial cells and monocytes; and induces plasminogen activators in endothelial cells, which are involved in the proteolytic degradation of extracellular matrix during the formation of capillaries. A number of isoforms of VEGF are known, which show comparable biological activity, but differ in the type of cells that secrete them and in their heparin-binding capacity. In addition, there are other members of the VEGF family, such as "Placenta Growth Factor" (PlGF) and VEGF-C.

VEGF receptors (VEGFR) are transmembranous receptor tyrosine kinases. They are characterized by an extracellular domain with seven immunoglobulin-like domains and an intracellular tyrosine kinase domain. Various types

of VEGF receptor are known, e.g. VEGFR-1 (also known as flt-1), VEGFR-2 (also known as KDR), and VEGFR-3.

A large number of human tumors, especially gliomas and carcinomas, express high levels of VEGF and its receptors.

5 This has led to the hypothesis that the VEGF released by tumor cells stimulates the growth of blood capillaries and the proliferation of tumor endothelium in a paracrine manner and through the improved blood supply, accelerate tumor growth. Increased VEGF expression could explain the

10 occurrence of cerebral edema in patients with glioma. Direct evidence of the role of VEGF as a tumor angiogenesis factor *in vivo* is shown in studies in which VEGF expression or VEGF activity was inhibited. This was achieved with anti-VEGF antibodies, with dominant-negative VEGFR-2 mutants which

15 inhibited signal transduction, and with antisense-VEGF RNA techniques. All approaches led to a reduction in the growth of glioma cell lines or other tumor cell lines *in vivo* as a result of inhibited tumor angiogenesis.

Angiogenesis is regarded as an absolute prerequisite

20 for tumors which grow beyond a diameter of about 1-2 mm; up to this limit, oxygen and nutrients may be supplied to the tumor cells by diffusion. Every tumor, regardless of its origin and its cause, is thus dependent on angiogenesis for its growth after it has reached a certain size.

25 Three principal mechanisms play an important part in the activity of angiogenesis inhibitors against tumors: 1) Inhibition of the growth of vessels, especially capillaries, into avascular resting tumors, with the result that there is no net tumor growth owing to the balance that

30 is achieved between cell death and proliferation; 2) Prevention of the migration of tumor cells owing to the absence of blood flow to and from tumors; and 3) Inhibition of endothelial cell proliferation, thus avoiding the paracrine growth-stimulating effect exerted on the

surrounding tissue by the endothelial cells which normally line the vessels. See R. Connell and J. Beebe, Exp. Opin. Ther. Patents, 11:77-114 (2001).

VEGF's are unique in that they are the only angiogenic growth factors known to contribute to vascular hyperpermeability and the formation of edema. Indeed, vascular hyperpermeability and edema that is associated with the expression or administration of many other growth factors appears to be mediated via VEGF production.

Inflammatory cytokines stimulate VEGF production. Hypoxia results in a marked upregulation of VEGF in numerous tissues, hence situations involving infarct, occlusion, ischemia, anemia, or circulatory impairment typically invoke VEGF/VPF-mediated responses. Vascular hyperpermeability, associated edema, altered transendothelial exchange and macromolecular extravasation, which is often accompanied by diapedesis, can result in excessive matrix deposition, aberrant stromal proliferation, fibrosis, etc. Hence, VEGF-mediated hyperpermeability can significantly contribute to disorders with these etiologic features. As such, regulators of angiogenesis have become an important therapeutic target.

Schipper US patent 3,226,394, issued Dec. 28, 1965, describes anthranilamides as CNS depressants. Japanese patent JP 2000256358 describes pyrazole derivatives that block the calcium release-activated calcium channel. EP application 9475000, published 6 October 1999, describes compounds as PGE₂ antagonists. PCT publication WO 96/41795, published 27 December 1996, describes benzamides as vasopressin antagonists. WO 01/29009 describes aminopyridines as KDR inhibitors. WO 01/30745 describes anthranilic acids as CGMP phosphodiesterase inhibitors. WO 00/02851, published 20 Jan 2000 describes arylsulfonylaminoaryl amides as guanylate cyclase activators. WO 98/45268 describes nicotinamide derivatives as PDE4

inhibitors. WO 98/24771 describes benzamides as vasopressin antagonists.

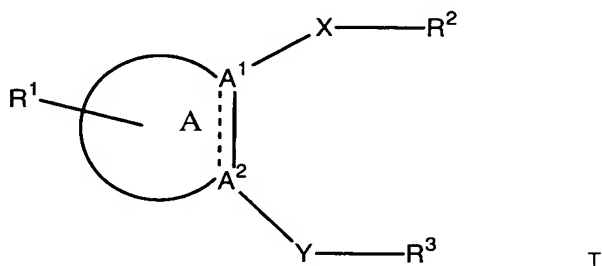
US Patent No. 5,532,358, issued July 2, 1996, describes the preparation of 2-(cyclopropylamino)-N-(2-methoxy-4-methyl-3-pyridinyl)-3-pyridinecarboxamide as an intermediate for HIV inhibitors. Triazine-substituted amines are described for their aggregating ability (J. Amer. Chem. Soc., 115:905-916 (1993). Substituted imidazolines were tested for their antidepressant activity in Ind. J. Het. Chem., 2:129-132 (1992). N-(4-Pyridyl)anthranilic amides were described in Chem Abstr. 97:109837 (1981). PCT publication WO 99/32477, published 1 July 1999, describes anthranilamides as anti-coagulants. US patent 6,140,351 describes anthranilamides as anti-coagulants. PCT publication WO 99/62885, published 9 December 1999, describes 1-(4-aminophenyl)pyrazoles as antiinflammatories. PCT publication WO 00/39111, published 6 July 2000, describes amides as factor Xa inhibitors. PCT publication WO 00/39117, published 6 July 2000, describes heteroaromatic amides as factor Xa inhibitors. PCT publication WO00/27819, published 18 May 2000, describes anthranilic acid amides as VEGF inhibitors. PCT publication WO 00/27820 published 18 May 2000, describes N-aryl anthranilic acid amides as VEGF inhibitors. 7-Chloroquinolinylamines are described in FR 2168227 as antiinflammatories. WO 01/55114, published 2 Aug. 2001, describes nicotinamides for the treatment of cancer. WO01/55115, published 2 Aug. 2001, describes nicotinamides for the treatment of apoptosis. WO 01/85715, published 15 November 2001, describes substituted pyridines and pyrimidines as anti-angiogenesis agents. PCT publication WO 01/85691 published 15 November 2001, describes anthranilic amides as VEGF inhibitors. PCT publication WO 01/85671 published 15 November 2001, describes anthranil amides as VEGF inhibitors. PCT publication WO 01/81311 published 1

November 2001, describes anthranilic amides as VEGF inhibitors.

However, compounds of the current invention have not been described as inhibitors of angiogenesis such as for the treatment of cancer.

DESCRIPTION OF THE INVENTION

A class of compounds useful in treating cancer and angiogenesis is defined by Formula I



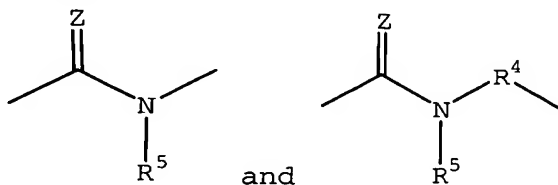
wherein each of A¹ and A² is independently C or N;

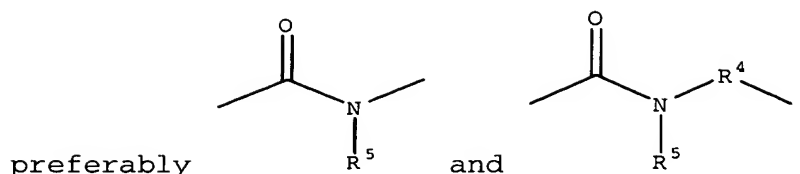
wherein A¹-A² together are part of a ring A selected from 5- or 6-membered heteroaryl,

more preferably 5-membered heteroaryl selected from thienyl, oxazolyl, imidazolyl, pyrrolyl, pyrazolyl, isoxazolyl, triazolyl, isothiazolyl, and

6-membered heteroaryl selected from pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl, even more preferably pyridyl or pyrimidinyl, most preferably pyridyl;

wherein X is selected from

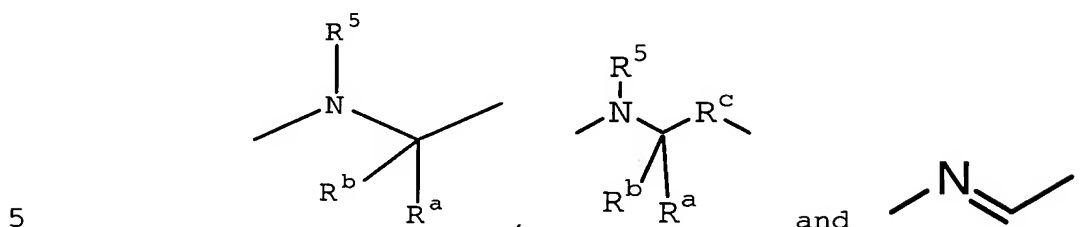




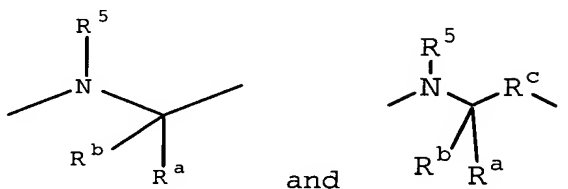
more preferably -C(O)-NH-;

wherein Z is oxygen or sulfur;

wherein Y is selected from



preferably selected from



more preferably -NH-CH₂-;

10 wherein R^a and R^b are independently selected from H, halo, and C₁₋₄-alkyl substituted with R¹, or wherein R^a and R^b together form C₃₋₄ cycloalkyl,

preferably H, halo, and C₁₋₂-alkyl substituted with R¹, or wherein R^a and R^b together form C₃₋₄ cycloalkyl, more preferably H, halo and C₁₋₂-alkyl,

15 even more preferably H;

wherein R^c is C₁₋₄ alkylene, where one of the CH₂ groups may be substituted with an oxygen atom or an -NH-,

preferably C₁₋₂ alkylene, where one of the CH₂ groups may be substituted with an oxygen atom or an -NH-,

20 more preferably -CH₂-;

wherein R¹ is one or more substituents independently selected from H, halo, -OR⁷, oxo, -SR⁷, -CO₂R⁷, -COR⁷, -CONR⁷R⁷, -NR⁷R⁷, -SO₂NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, cycloalkyl, optionally substituted phenylalkylene,

optionally substituted 5-6 membered heterocyclyl,
optionally substituted heteroarylalkylenyl, optionally
substituted phenyl, lower alkyl, cyano, lower
hydroxyalkyl, lower carboxyalkyl, nitro, lower alkenyl,
5 lower alkynyl, lower aminoalkyl, lower alkylaminoalkyl
and lower haloalkyl;
preferably H, halo, -OR⁷, oxo, -SR⁷, -CO₂R⁷, -CONR⁷R⁷,
-COR⁷, -NR⁷R⁷, -SO₂NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷,
cycloalkyl, optionally substituted 5-6 membered
10 heterocyclyl, optionally substituted phenyl, C₁-C₂-
alkyl, cyano, C₁-C₂-hydroxyalkyl, C₁-C₃-carboxyalkyl,
nitro, C₂-C₃-alkenyl, C₂-C₃-alkynyl and C₁-C₂-haloalkyl,
more preferably H, halo, -OR⁷, -SR⁷, -CO₂R⁷, -CONR⁷R⁷,
-COR⁷, -NR⁷R⁷, -SO₂NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷,
15 cycloalkyl, optionally substituted 5-6 membered
heterocyclyl, optionally substituted phenyl, C₁-2-
alkyl, cyano, C₁-2-hydroxyalkyl, C₁-3-carboxyalkyl,
nitro, C₂-3-alkenyl, C₂-3-alkynyl and C₁-2-haloalkyl,
additionally preferred are H, chloro, fluoro,
20 bromo, amino, hydroxy, methyl, ethyl, propyl,
trifluoromethyl, methoxy, ethoxy,
trifluoromethoxy, carboxymethyl, unsubstituted or
substituted phenyl and unsubstituted or
substituted heteroaryl selected from thienyl,
25 furanyl, pyridyl, imidazolyl, and pyrazolyl;
wherein R² is selected from
a) substituted or unsubstituted 6-10 membered aryl,
b) substituted or unsubstituted 5-6 membered
heterocyclyl,
30 c) substituted or unsubstituted 9-11 membered fused
heterocyclyl,
d) cycloalkyl, and
e) cycloalkenyl,

preferably substituted or unsubstituted aryl selected
from phenyl, naphthyl, indenyl and
tetrahydronaphthyl, substituted or unsubstituted 5-
6 membered heteroaryl, and substituted or
5 unsubstituted 9-10 membered fused heteroaryl,
more preferably phenyl, indazolyl, indolyl, 2,1,3-
benzothiadiazolyl, isoquinolyl, quinolyl, and
quinazolinyl,
even more preferably phenyl, indazolyl, indolyl,
10 isoquinolyl and quinolyl;
wherein substituted R² is substituted with one or more
substituents independently selected from halo, -OR⁷,
-SR⁷, -SO₂R⁷, -CO₂R⁷, -CONR⁷R⁷, -COR⁷, -NR⁷R⁷, -SO₂NR⁷R⁷,
-NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, -NH(C₁-C₄ alkyleneR⁷),
15 optionally substituted cycloalkyl, optionally
substituted 5-6 membered heterocyclyl, optionally
substituted phenyl, lower alkyl substituted with R¹,
cyano, nitro, lower alkenyl and lower alkynyl,
preferably halo, -OR⁷, -SR⁷, -SO₂R⁷, -CO₂R⁷, -CONR⁷R⁷,
20 -COR⁷, -NR⁷R⁷, -NH(C₁-C₂-alkyleneR⁷), -(C₁-C₂-
alkylene)NR⁷R⁷, -SO₂NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷,
optionally substituted cycloalkyl, optionally
substituted 5-6 membered heterocyclyl, optionally
substituted phenyl, optionally substituted phenyl-C₁-
25 C₂-alkylene, optionally substituted 5-6 membered
heterocyclyl-C₁-C₂-alkylene, C₁-C₂-alkyl, cyano, C₁-C₂-
hydroxyalkyl, nitro and C₁-C₂-haloalkyl,
more preferably halo, -OR⁷, -SR⁷, -CO₂R⁷, -CONR⁷R⁷,
-COR⁷, -NR⁷R⁷, -NH(C₁-C₂-alkylene-R⁷), -(C₁-C₂-
30 alkylene)NR⁷R⁷, -SO₂NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷,
optionally substituted cycloalkyl, optionally
substituted 5-6 membered heterocyclyl, optionally
substituted phenyl, optionally substituted phenyl-
C₁-C₂-alkylene, optionally substituted 5-6 membered

heterocyclyl-C₁-C₂-alkylenyl, C₁-C₂-alkyl, cyano, C₁-C₂-hydroxyalkyl, nitro and C₁-C₂-haloalkyl, additionally preferred are chloro, fluoro, amino, hydroxy, cyclohexyl, phenylmethyl, morpholinylmethyl, methylpiperidinylmethyl, methylpiperazinylmethyl, ethyl, propyl, trifluoromethyl, phenyloxy, methoxy and ethoxy; wherein R³ is selected from aryl, preferably phenyl;

wherein R³ is substituted with one or more substituents independently selected from halo, -OR⁷, -SR⁷, -CO₂R⁷, -CONR⁷R⁷, -COR⁷, -NR⁷R⁷, -SO₂NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, cycloalkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted heteroarylalkylenyl, optionally substituted phenyl, lower alkyl substituted with R¹, cyano, nitro, lower alkenyl and lower alkynyl, preferably halo, -OR⁷, -SR⁷, -CO₂R⁷, -CONR⁷R⁷, -COR⁷, -NR⁷R⁷, -SO₂NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, cyano, lower hydroxyalkyl, lower aminoalkyl and nitro, more preferably halo, -OR⁷, -CONR⁷R⁷, -NR⁷R⁷, -SO₂NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, cyano, amino-C₁-C₂-alkyl, hydroxy-C₁-C₂-alkyl, and nitro, even more preferably chloro, fluoro, amino, hydroxy, hydroxymethyl, aminomethyl, nitro, methoxy and ethoxy;

wherein R⁴ is independently selected from C₂-C₄ alkylenyl, C₂-C₄ alkenylenyl and C₂-C₄ alkynylenyl, where one of the CH₂ groups may be substituted with an oxygen atom or an -NH-, preferably C₂₋₃-alkylenyl, where one of the CH₂ groups may be substituted with an oxygen atom or an -NH-;

wherein R⁵ is selected from H, lower alkyl, phenyl and lower aralkyl, preferably H or C₁₋₂-alkyl;

wherein R^6 is selected from H or C_{1-6} -alkyl; and
 wherein R^7 is selected from H, lower alkyl, phenyl, 5-6
 membered heterocyclyl, C_3 - C_6 cycloalkyl, and lower
 haloalkyl,

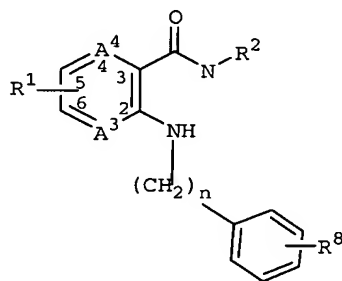
5 preferably H, C_{1-2} -alkyl, phenyl, C_3 - C_6 cycloalkyl and C_{1-2} -
 haloalkyl,

more preferably H, methyl, ethyl, cyclopropyl,
 cyclohexyl and trifluoromethyl;

and pharmaceutically acceptable salts thereof;

10 provided R^3 is substituted with one or more radicals
 selected from $-OR^7$, $-SR^7$, $-CO_2R^7$, $-CONR^7R^7$, $-COR^7$, $-NR^7R^7$,
 lower aminoalkyl, lower alkylaminoalkyl, $-SO_2NR^7R^7$,
 $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, cyano or lower hydroxyalkyl.

The invention also relates to compounds of Formula II

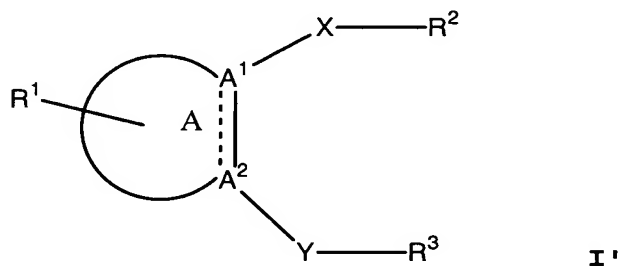


II

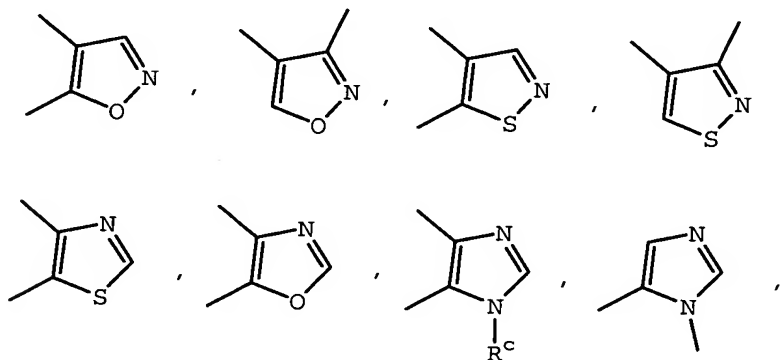
15 wherein each of A^3 and A^4 is independently C or N, provided
 at least one of A^3 and A^4 is N; wherein n is 1-2; wherein R^1
 is one or more substituents independently selected from H,
 20 chloro, fluoro, bromo, amino, hydroxy, methyl, ethyl,
 propyl, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy,
 carboxymethyl, unsubstituted or substituted phenyl and
 unsubstituted or substituted heteroaryl selected from
 thienyl, furanyl, pyridyl, imidazolyl and pyrazolyl; wherein
 25 R^2 is selected from phenyl, isoquinolyl and quinolyl, where
 R^2 is unsubstituted or substituted with one or more
 substituents selected from chloro, fluoro, amino, hydroxy,
 cyclohexyl, phenylmethyl, morpholinylmethyl,
 methylpiperdinylmethyl, methylpiperazinylmethyl, ethyl,

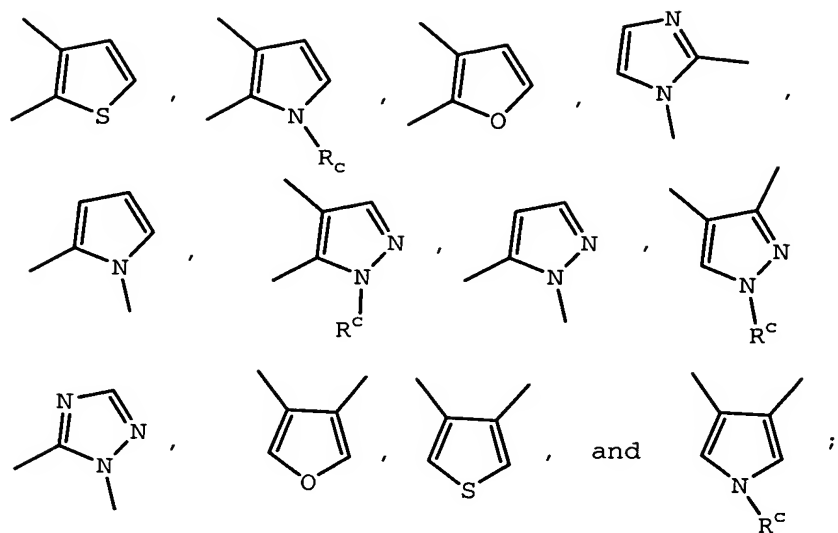
propyl, trifluoromethyl, phenyloxy, methoxy and ethoxy; and wherein R^8 is one or more substituents independently selected from chloro, fluoro, methyl, cyano, amino, hydroxy, aminomethyl, hydroxymethyl, nitro, methoxy and ethoxy; and
 5 pharmaceutically acceptable salts thereof; provided R^8 is one or more radicals selected from amino, cyano, aminomethyl, hydroxymethyl, hydroxy, methoxy and ethoxy.

A class of compounds useful in treating cancer and
 10 angiogenesis is defined by Formula I'



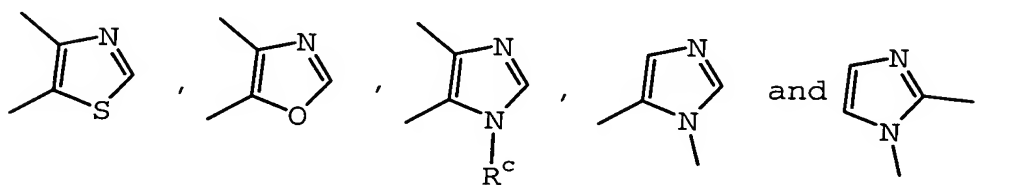
wherein each of A^1 and A^2 is independently C or N;
 wherein A^1 - A^2 form part of a ring A selected from 5- or 6-
 15 membered heteroaryl,
 preferably
 I) 5-membered heteroaryl selected from thienyl,
 furanyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl,
 pyrazolyl, isoxazolyl, triazolyl and isothiazolyl,
 20 even more preferably 5-membered heteroaryl selected
 from





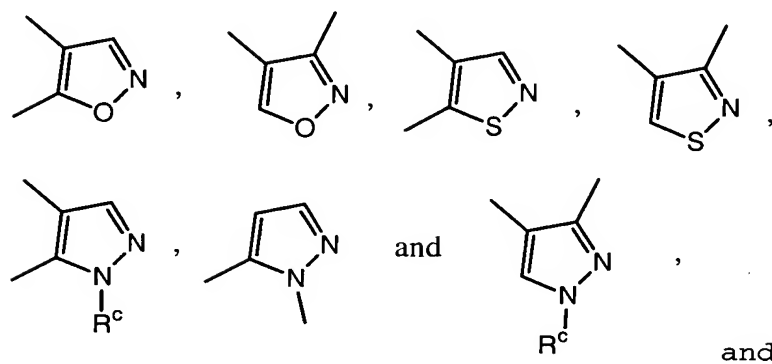
specifically

A)



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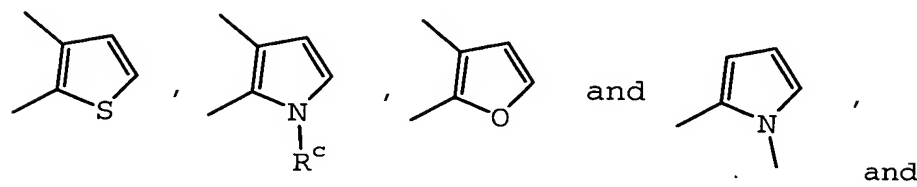
B)



and

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C)



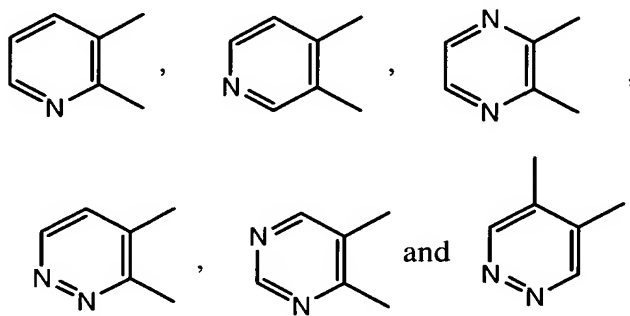
and

II) preferably 6-membered heteroaryl selected from pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, and triazinyl,

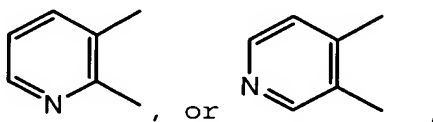
even more preferably 6-membered heteroaryl selected

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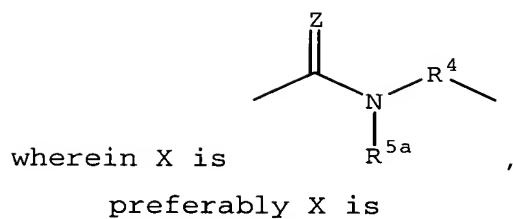
from



specifically, pyridyl and pyrimidinyl,
more specifically

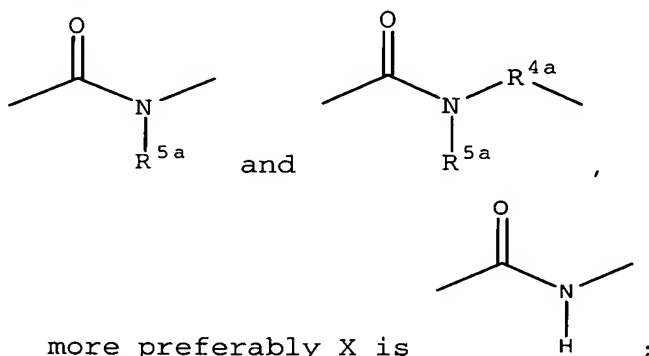


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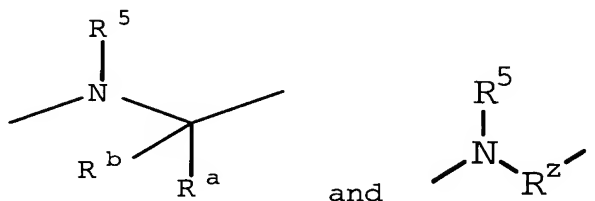
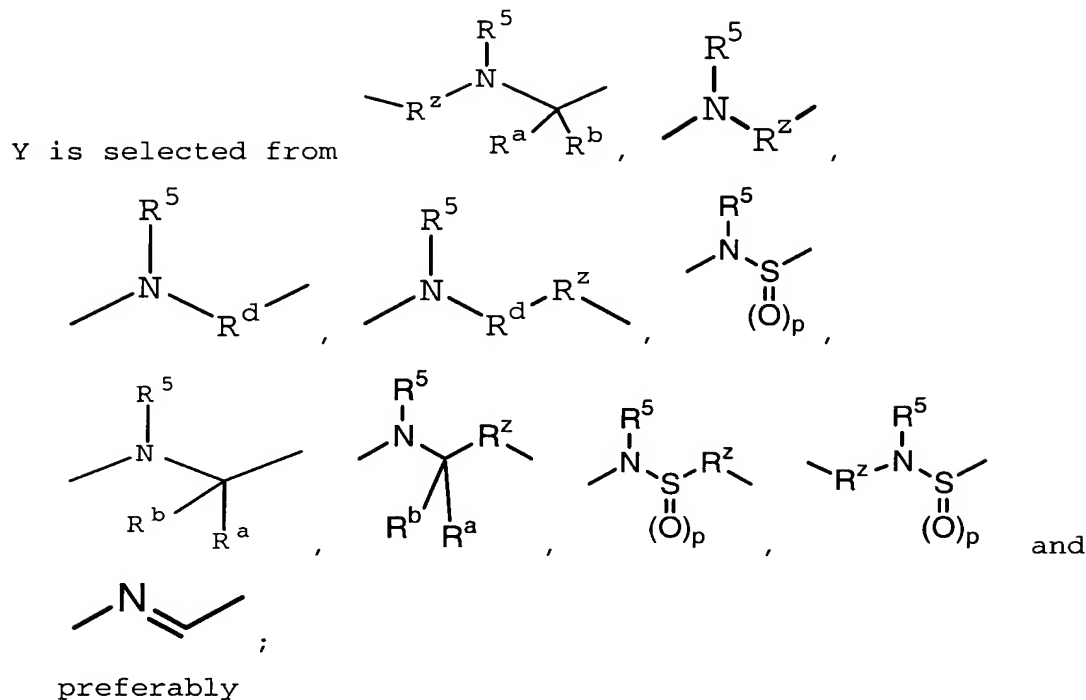
wherein X is

preferably X is



more preferably X is

15 wherein Z is oxygen or sulfur;



more preferably -NH-CH₂-;

wherein p is 0 to 2,

preferably 2;

- 10 wherein R^a and R^b are independently selected from H, halo, cyano, -NHR⁶ and C₁₋₄-alkyl substituted with R¹, or wherein R^a and R^b together form C₃-C₆ cycloalkyl; preferably H, halo, and C₁₋₂-alkyl substituted with R¹, or wherein R^a and R^b together form C₃-C₄ cycloalkyl,
- 15 more preferably H, chloro, fluoro and C₁-C₂-alkyl, even more preferably H;

wherein R^z is selected from C₂-C₆-alkylenyl, where one of the CH₂ groups may be replaced with an oxygen atom or an -NH- group; wherein one of the CH₂ groups may be substituted

with one or two radicals selected from halo, cyano, -NHR^6 and C_{1-4} -alkyl substituted with R^1 ; preferably $\text{C}_2\text{-C}_3$ alkylene, where one of the CH_2 groups may be replaced with an oxygen atom or an -NH- ,
5 more preferably $\text{-(CH}_2\text{)}_2\text{-}$;
wherein R^d is optionally substituted cycloalkyl, preferably C_{3-6} -cycloalkyl;
wherein R^1 is one or more substituents independently selected from H, halo, -OR^7 , oxo, -SR^7 , $\text{-CO}_2\text{R}^7$, -COR^7 , $\text{-CONR}^7\text{R}^7$,
10 $\text{-NR}^7\text{R}^7$, $\text{-SO}_2\text{NR}^7\text{R}^7$, $\text{-NR}^7\text{C(O)OR}^7$, $\text{-NR}^7\text{C(O)R}^7$, optionally substituted cycloalkyl, optionally substituted phenylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted phenyl, lower alkyl, cyano, lower
15 hydroxyalkyl, lower carboxyalkyl, nitro, lower alkenyl, lower alkynyl, lower aminoalkyl, lower alkylaminoalkyl and lower haloalkyl, preferably H, halo, -OR^7 , oxo, -SR^7 , $\text{-CO}_2\text{R}^7$, $\text{-CONR}^7\text{R}^7$, -COR^7 , $\text{-NR}^7\text{R}^7$, $\text{-SO}_2\text{NR}^7\text{R}^7$, $\text{-NR}^7\text{C(O)OR}^7$, $\text{-NR}^7\text{C(O)R}^7$,
20 optionally substituted C_{3-6} -cycloalkyl, optionally substituted phenyl- C_{1-4} -alkyl, optionally substituted 4-6 membered heterocyclyl, optionally substituted phenyl, optionally substituted 4-6 membered heterocyclyl- C_{1-4} -alkyl, C_{1-6} -alkyl, cyano, C_{1-4} -
25 hydroxyalkyl, C_{1-4} -carboxyalkyl, nitro, C_{2-3} -alkenyl, C_{2-3} -alkynyl and C_{1-4} -haloalkyl, more preferably H, halo, hydroxy, C_{1-2} -alkoxy, C_{1-2} -haloalkoxy, amino, C_{1-2} -alkylamino, optionally substituted 4-6 membered heterocyclyl- C_{1-2} -alkylamino, aminosulfonyl, C_{3-6} -cycloalkyl,
30 optionally substituted 4-6 membered heterocyclyl, optionally substituted phenyl, C_{1-4} -alkyl, cyano, C_{1-2} -hydroxyalkyl, C_{1-3} -carboxyalkyl, nitro, C_{2-3} -alkenyl, C_{2-3} -alkynyl and C_{1-2} -haloalkyl, and

even more preferably H, chloro, fluoro, bromo,
hydroxy, methoxy, ethoxy, trifluoromethoxy, oxo,
amino, dimethylamino, aminosulfonyl,
carboxymethyl, cyclopropyl, optionally
5 substituted phenyl, methyl, ethyl, propyl, cyano,
hydroxymethyl, nitro, propenyl, propynyl,
trifluoromethyl and unsubstituted or substituted
heteroaryl selected from
thienyl, furanyl, pyridyl, imidazolyl and
10 pyrazolyl;
wherein R² is selected from
a) substituted or unsubstituted 6-10 membered aryl,
preferably phenyl, naphthyl, benzodioxolyl, indanyl,
indenyl and tetrahydronaphthyl,
15 more preferably phenyl, indanyl,
tetrahydronaphthyl, and naphthyl,
b) substituted or unsubstituted 5-6 membered
heterocyclyl,
preferably 5-6 membered heteroaryl,
20 more preferably isoxazolyl, pyrazolyl, thiazolyl,
thiadiazolyl, thienyl, pyridyl, pyrimidinyl,
pyridazinyl, imidazolyl, oxazolyl, furyl and
pyrrolyl,
c) substituted or unsubstituted 9-14 membered bicyclic or
25 tricyclic heterocyclyl,
preferably 9-10 membered bicyclic or 13-14 membered
tricyclic heterocyclyl,
more preferably indazolyl, indolyl, isoindolyl,
2,3-dihydro-1H-indolyl, naphthyridinyl, 2,1,3-
30 benzothiadiazolyl, isoquinolyl, quinolyl, 1,2-
dihydroquinolyl, 1,2,3,4-tetrahydro-isoquinolyl,
2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl,
5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinolyl,
3,4-dihydro-2H-benzo[1,4]oxazinyl, benzothienyl,

tetrahydroquinolyl, benzofuryl, benzimidazolyl, benzoxazolyl, benzthiazolyl, benzodioxanyl and quinazolinyl,

even more preferably 9-10 membered bicyclic or 13-14 membered tricyclic saturated or partially unsaturated heterocyclyl,

specifically 1,2-dihydroquinolyl, 1,2,3,4-tetrahydro-isoquinolyl, 1,2,3,4-tetrahydro-quinolyl, 2,3-dihydro-1H-indolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinolyl, 3,4-dihydro-2H-benzo[1,4]oxazinyl, and benzo[1,4]dioxanyl;

d) cycloalkyl,

preferably C₃₋₆-cycloalkyl,

more preferably cyclohexyl, and

e) cycloalkenyl,

wherein substituted R² is substituted with one or more

substituents independently selected from halo, -OR⁷, oxo, -SR⁷, -CO₂R⁷, -CONR⁷R⁷, -COR⁷, -NR⁷R⁷, -NH(C₁-C₄

alkylenylR⁹), -SO₂R⁷, -SO₂NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, -NR⁷C(O)NR⁷R⁷, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted phenyl, halosulfonyl, cyano,

alkylaminoalkoxy, alkylaminoalkoxyalkoxy, nitro, lower alkyl substituted with R¹, lower alkenyl substituted with R¹, and lower alkynyl substituted with R¹,

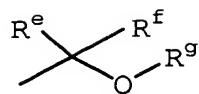
preferably halo, -OR⁷, oxo, -SR⁷, -SO₂R⁷, -CO₂R⁷,

-CONR⁷R⁷, -COR⁷, -NR⁷R⁷, -NH(C₁-C₂-alkylenylR⁹),

-(C₁-C₂-alkylenyl)NR⁷R⁷, -SO₂NR⁷R⁷, -NR⁷C(O)OR⁷,

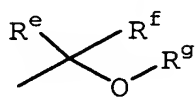
-NR⁷C(O)R⁷, C₁-C₆-alkylamino-C₁-C₆-alkoxy, C₁-C₆-

alkylamino-C₁-C₆-alkoxy-C₁-C₆-alkoxy, halosulfonyl, optionally substituted 4-6 membered heterocyclyl-carbonylalkyl, C₁₋₄-alkoxycarbonylamino-C₁₋₆-alkyl,



, optionally substituted C₃₋₆-cycloalkyl, optionally substituted 4-6 membered heterocyclyl, optionally substituted phenyl, optionally substituted phenyl-C₁₋₆-alkylenyl, optionally substituted 4-6 membered heterocyclyl-C_{1-C₆}-alkylenyl, 4-6 membered heterocyclyl-C_{2-C₆}-alkenylenyl, C₁₋₄-alkyl, cyano, C₁₋₄-hydroxyalkyl, nitro and C₁₋₄-haloalkyl, more preferably halo, C₁₋₄-alkyl, optionally substituted C₃₋₆-cycloalkyl, optionally substituted phenyl, optionally substituted phenyl-C_{1-C₄}-alkylenyl, C₁₋₂-haloalkoxy, optionally substituted phenyloxy, optionally substituted 4-6 membered heterocyclyl-C_{1-C₄}-alkylenyl, optionally substituted 4-6 membered heterocyclyl-C_{2-C₄}-alkenylenyl, optionally substituted 4-6 membered heterocyclyl, optionally substituted 4-6 membered heterocycliloxy, optionally substituted 4-6 membered heterocyclylsulfonyl, optionally substituted 4-6 membered heterocyclylamino, optionally substituted 4-6 membered heterocyclylcarbonyl, optionally substituted 4-6 membered heterocyclyl-C₁₋₄-alkylcarbonyl, C₁₋₂-haloalkyl, C₁₋₄-aminoalkyl, nitro, amino, hydroxy, cyano, aminosulfonyl, C₁₋₂-alkylsulfonyl, halosulfonyl, C₁₋₄-alkylcarbonyl, C₁₋₃-alkylamino-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkoxy, C₁₋₃-alkylamino-C₁₋₃-alkoxy-C₁₋₃-alkoxy, C₁₋₄-alkoxycarbonyl, C₁₋₄-

alkoxycarbonylamino-C₁₋₄-alkyl, C₁₋₄-

hydroxyalkyl,  and C₁₋₄-alkoxy, even more preferably bromo, chloro, fluoro, iodo, nitro, amino, cyano, aminoethyl, Boc-aminoethyl, hydroxy, aminosulfonyl, 4-methylpiperazinylsulfonyl, cyclohexyl, phenyl, phenylmethyl, morpholinylmethyl, methylpiperazinylmethyl, morpholinylethyl, methylpiperazinylpropyl, 1-(4-morpholinyl)-2,2-dimethylpropyl, piperidinylmethyl, morpholinylpropyl, methylpiperidinylmethyl, piperidinylethyl, piperidinylpropyl, pyrrolidinylpropyl, pyrrolidinylpropenyl, pyrrolidinylbutenyl, fluorosulfonyl, methylsulfonyl, methylcarbonyl, piperidinylmethylcarbonyl, methylpiperazinylcarbonylethyl, methoxycarbonyl, 3-ethoxycarbonyl-2-methylfur-5-yl, methylpiperazinyl, methylpiperidyl, 1-methyl-(1,2,3,6-tetrahydropyridyl), imidazolyl, morpholinyl, 4-trifluoromethyl-1-piperidinyl, hydroxybutyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, sec-butyl, trifluoromethyl, pentafluoroethyl, nonafluorobutyl, dimethylaminopropyl, 1,1-di(trifluoromethyl)-1-hydroxymethyl, trifluoromethoxy, 1,1-di(trifluoromethyl)-1-(piperidinylethoxy)methyl, 1,1-di(trifluoromethyl)-1-(methoxyethoxyethoxy)methyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-aminoethyl, 2-aminoethyl, 1-(N-isopropylamino)ethyl, 2-

(N-isopropylamino)ethyl,
dimethylaminoethoxy, 4-chlorophenoxy,
phenyloxy, 1-methylpiperidin-4-yloxy,
isopropoxy, methoxy and ethoxy;

5 wherein R³ is selected from unsubstituted or substituted
aryl,

preferably substituted phenyl,

wherein substituted R³ is substituted with one or more
substituents independently selected from halo, -OR⁷,
10 -SR⁷, -SO₂R⁷, -CO₂R⁷, -CONR⁷R⁷, -COR⁷, -NR⁷R⁷, -SO₂NR⁷R⁷,
-NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, cycloalkyl, optionally
substituted heterocyclyl, optionally substituted
phenyl, nitro, alkylaminoalkoxyalkoxy, cyano,
alkylaminoalkoxy, lower alkyl substituted with R¹,
15 lower alkenyl substituted with R¹, and lower alkynyl
substituted with R¹;

preferably halo, -OR⁷, -SR⁷, -CO₂R⁷, -CONR⁷R⁷, -COR⁷,
-NR⁷R⁷, -SO₂NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, C₃₋₆-
cycloalkyl, optionally substituted 4-6 membered
20 heterocyclyl, optionally substituted phenyl, C₁₋₄-
alkyl, C₁₋₄-aminoalkyl, cyano, C₁₋₄-hydroxyalkyl,
nitro and C₁₋₄-haloalkyl,

more preferably halo, hydroxy, C₁₋₄-alkyl, C₁₋₂-
alkoxy, optionally substituted 4-6 membered
25 heterocyclyl-C₁₋₂-alkoxy, amino, C₁₋₂-alkylamino,
aminosulfonyl, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, C₃₋₆-
cycloalkyl, optionally substituted 4-6 membered
heterocyclyl, optionally substituted phenyl,
nitro, C₁₋₂-alkylamino-C₁₋₂-alkoxy-C₁₋₂-alkoxy,
30 cyano, C₁₋₂-alkylamino-C₁₋₂-alkoxy, C₁₋₂-alkylamino-
C₁₋₂-alkyl, C₁₋₂-alkylamino-C₂₋₃-alkynyl, C₁₋₂-
hydroxyalkyl, C₁₋₂-aminoalkyl, C₁₋₂-haloalkyl,
optionally substituted 4-6 membered heterocyclyl-

C₂₋₃-alkenyl, and optionally substituted 4-6
membered heterocyclyl-C₂₋₃-alkynyl,
even more preferably chloro, fluoro, bromo,
hydroxy, methoxy, ethoxy, amino,
5 dimethylamino, diethylamino, 1-
methypiperidinylmethoxy, aminosulfonyl,
cyclohexyl, dimethylaminopropynyl,
dimethylaminoethoxy, 3-(4-morpholinyl)propyn-
1-yl, dimethylaminoethoxyethoxy, optionally
10 substituted piperidinyl, morpholinyl,
optionally substituted piperazinyl, optionally
substituted phenyl, methyl, ethyl, propyl,
cyano, hydroxymethyl, aminomethyl, nitro and
trifluoromethyl;

15 wherein R⁴ is independently selected from a direct bond, C₂₋₄-
alkylenyl, C₂₋₄-alkenylenyl and C₂₋₄-alkynylenyl, where
one of the CH₂ groups may be substituted with an oxygen
atom or -NH-, wherein R⁴ is optionally substituted with
hydroxy,

20 preferably a direct bond or R^{4a};
wherein R^{4a} is selected from C₂₋₄-alkylenyl where one of the
CH₂ groups may be replaced with an oxygen atom or -NH-,
wherein R^{4a} is optionally substituted with hydroxy,



25 wherein R⁵ is selected from H, lower alkyl, phenyl and lower
aralkyl,

preferably H, methyl or ethyl,

more preferably H;

wherein R^{5a} is selected from H, lower alkyl, phenyl and

30 lower aralkyl,

preferably H, methyl or ethyl,

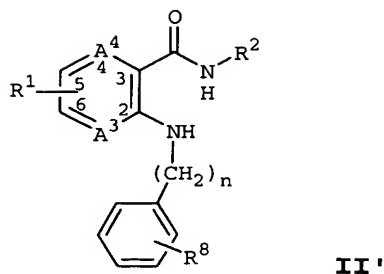
more preferably H;

wherein R⁶ is selected from H or C₁₋₆-alkyl,

preferably H or C₁₋₂ alkyl;
wherein R⁷ is selected from H, lower alkyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted C₃-C₆-cycloalkyl, optionally substituted phenyl-C₁₋₆-alkyl, optionally substituted heterocyclyl-C₁₋₆-alkyl, optionally substituted C₃-C₆ cycloalkyl-C₁₋₆-alkyl, lower alkylaminoalkyl, and lower haloalkyl,
preferably H, C₁₋₄-alkyl, optionally substituted phenyl, optionally substituted phenyl-C₁₋₄-alkyl, optionally substituted 4-6 membered heterocyclyl, optionally substituted 4-6 membered heterocyclyl-C₁₋₄-alkyl, optionally substituted C₃-C₆ cycloalkyl, C₁₋₂-alkylamino-C₁₋₄-alkyl and C₁₋₂-haloalkyl,
more preferably H, methyl, phenyl, cyclopropyl, cyclohexyl, benzyl, morpholinylmethyl, 4-methylpiperazinylmethyl, 4-methylpiperidinylmethyl, 4-morpholinylmethyl, 4-morpholinylethyl, 1-(4-morpholinyl)-2,2-dimethylpropyl, 1-piperdinylethyl, 1-piperdinylpropyl, 1-pyrrolidinylpropyl and trifluoromethyl;
wherein R^c is selected from H, methyl and optionally substituted phenyl; and
wherein R^e and R^f are independently selected from H and C₁₋₂-haloalkyl, preferably -CF₃;
wherein R^g is selected from H, C₁₋₆-alkyl, optionally substituted phenyl-C₁₋₆-alkyl, optionally substituted 4-6 membered heterocyclyl, optionally substituted 4-6 membered heterocyclyl-C₁₋₆-alkyl, C₁₋₄-alkoxy-C₁₋₄-alkyl and C₁₋₄-alkoxy-C₁₋₄-alkoxy-C₁₋₄-alkyl,
preferably H, C₁₋₃-alkyl, optionally substituted phenyl-C₁₋₃-alkyl, optionally substituted 4-6 membered heterocyclyl-C₁₋₃-alkyl, C₁₋₃-alkoxy-C₁₋₃-alkyl and C₁₋₃-alkoxy-C₁₋₃-alkoxy-C₁₋₃-alkyl; and

- wherein R⁹ is selected from H, optionally substituted phenyl, optionally substituted 4-6 membered heterocyclyl and C₃-C₆ cycloalkyl;
provided R² is not 3-trifluoromethylphenyl when A is
- 5 pyridyl, when X is -C(O)NH-, when Y is -NH-CH₂-, when R¹ is H and R³ is 3-(N-methylamino-carbonyl)phenyl, 4-hydroxyphenyl, 3-hydroxyphenyl or phenyl;
further provided R² is not substituted with -SO₂NR⁷R⁷ when Y is -NHSO₂-;
- 10 further provided R² is not 3-trifluoromethylphenyl when A is pyridyl, when X is -C(O)NH-, when Y is -N(benzyl)-CH₂-, when R¹ is H and when R³ is phenyl;
further provided R² is not cyclohexyl when A is pyridyl, when X is -C(O)NH-, when Y is -NH-CH₂-, when R¹ is H
- 15 and when R³ is 2-methoxyphenyl or 3-methoxyphenyl;
further provided R¹ is not 2-hydroxymethylpyrrol-5-yl when A is pyridyl;
further provided R¹ is not 4-(methoxyaminocarbonylamino)phenyl when A is thienyl;
- 20 further provided R¹ is not 2-pyridylmethoxy when A is pyrimidyl, when X is -C(O)NH-, and when Y is -NH-CH₂-;
further provided R¹ is not 4-methylpiperidyl when A is pyrimidyl, when X is -C(O)NH-, when Y is -NH-CH₂-, and when R³ is 3-chloro-4-methoxyphenyl;
- 25 further provided R¹ is not bromo when A is pyrimidyl, when X is -C(O)NH-CH₂-, when Y is -NH-CH₂-, and when R³ is 3-chloro-4-methoxyphenyl;
further provided R² is not 2-chloro-3-pyridyl when A is pyridyl; and
- 30 further provided R² is not 2-methoxyphenyl when A is pyridyl, when X is -C(O)NH-, when Y is -NH-CH₂-, when R¹ is H and R³ is phenyl.

The invention also relates to compounds of Formula II'



- wherein each of A³ and A⁴ is independently CH or N, provided
at least one of A³ and A⁴ is N;
- 5 wherein n is 1-2;
- wherein R¹ is one or more substituents independently
selected from H, chloro, fluoro, bromo, hydroxy, methoxy,
ethoxy, trifluoromethoxy, oxo, amino, dimethylamino,
aminosulfonyl, carboxymethyl, cyclopropyl, optionally
10 substituted phenyl, methyl, ethyl, propyl, cyano,
hydroxymethyl, nitro, propenyl, propynyl,
morpholinylethylamino, trifluoromethyl and unsubstituted
or substituted heteroaryl selected from thienyl, furanyl,
pyridyl, imidazolyl and pyrazolyl;
- 15 wherein R² is a substituted or unsubstituted ring selected
from phenyl, tetrahydronaphthyl, indanyl, benzodioxolyl,
indenyl, naphthyl, isoxazolyl, pyrazolyl, thiazolyl,
thiadiazolyl, thienyl, pyridyl, pyrimidinyl, pyridazinyl,
1,2-dihydroquinolyl, 1,2,3,4-tetrahydro-isoquinolyl,
20 1,2,3,4-tetrahydro-quinolyl, isoquinolyl, quinolyl,
indolyl, isoindolyl, 2,3-dihydro-1H-indolyl,
naphthyridinyl, quinoxalinyl, 2,3,4,4a,9,9a-hexahydro-1H-
3-aza-fluorenyl, 5,6,7-trihydro-1,2,4-triazolo[3,4-
a]isoquinolyl, indazolyl, 2,1,3-benzothiadiazolyl, 3,4-
25 dihydro-2H-benzo[1,4]oxazinyl, benzodioxanyl,
benzothienyl, benzofuryl, benzimidazolyl, benzoxazolyl
and benzthiazolyl;
- wherein substituted R² is substituted with one or more
substituents independently selected from bromo,

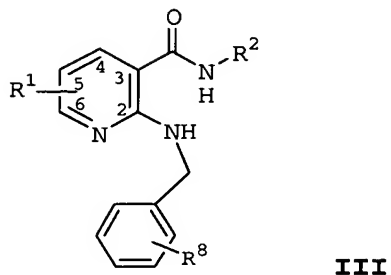
chloro, fluoro, iodo, nitro, amino, cyano, aminoethyl,
Boc-aminoethyl, hydroxy, oxo, aminosulfonyl, 4-
methylpiperazinylsulfonyl, cyclohexyl, phenyl,
phenylmethyl, morpholinylmethyl, 1-methylpiperazin-4-
5 ylmethyl, 1-methylpiperazin-4-ylpropyl,
morpholinylpropyl, piperidin-1-ylmethyl, 1-
methylpiperidin-4-ylmethyl, 2-methyl-2-(1-
methylpiperidin-4-yl)ethyl, morpholinylethyl, 1-(4-
morpholinyl)-2,2-dimethylpropyl, piperidin-4-ylethyl,
10 1-Boc-piperidin-4-ylethyl, piperidin-1-ylethyl, 1-Boc-
piperidin-4-ylethyl, piperidin-4-ylmethyl, 1-Boc-
piperidin-4-ylmethyl, piperidin-4-ylpropyl, 1-Boc-
piperidin-4-ylpropyl, piperidin-1-ylpropyl,
pyrrolidin-1-ylpropyl, pyrrolidin-2-ylpropyl, 1-Boc-
15 pyrrolidin-2-ylpropyl, pyrrolidin-1-ylmethyl,
pyrrolidin-2-ylmethyl, 1-Boc-pyrrolidin-2-ylmethyl,
pyrrolidinylpropenyl, pyrrolidinylbutenyl,
fluorosulfonyl, methylsulfonyl, methylcarbonyl, Boc,
piperidin-1-ylmethylcarbonyl, 4-methylpiperazin-1-
20 ylcarbonylethyl, methoxycarbonyl, aminomethylcarbonyl,
dimethylaminomethylcarbonyl, 3-ethoxycarbonyl-2-
methyl-fur-5-yl, 4-methylpiperazin-1-yl, 4-methyl-1-
piperidyl, 1-Boc-4-piperidyl, piperidin-4-yl, 1-
methylpiperidin-4-yl, 1-methyl-(1,2,3,6-
25 tetrahydropyridyl), imidazolyl, morpholinyl, 4-
trifluoromethyl-1-piperidinyl, hydroxybutyl, methyl,
ethyl, propyl, isopropyl, butyl, tert-butyl, sec-
butyl, trifluoromethyl, pentafluoroethyl,
nonafluorobutyl, dimethylaminopropyl, 1,1-
30 di(trifluoromethyl)-1-hydroxymethyl, 1,1-
di(trifluoromethyl)-1-(piperidinylethoxy)methyl, 1,1-
di(trifluoromethyl)-1-(methoxyethoxyethoxy)methyl, 1-
hydroxyethyl, 2-hydroxyethyl, trifluoromethoxy, 1-
aminoethyl, 2-aminoethyl, 1-(N-isopropylamino)ethyl,

2-(N-isopropylamino)ethyl, dimethylaminoethoxy, 4-chlorophenoxy, phenyloxy, azetidin-3-ylmethoxy, 1-Boc-azetidin-3-ylmethoxy, pyrrol-2-ylmethoxy, 1-Boc-pyrrol-2-ylmethoxy, pyrrol-1-ylmethoxy, 1-methyl-pyrrol-2-ylmethoxy, 1-isopropyl-pyrrol-2-ylmethoxy, 1-Boc-piperdin-4-ylmethoxy, piperdin-4-ylmethoxy, 1-methylpiperdin-4-yloxy, isopropoxy, methoxy and ethoxy; and

wherein R⁸ is one or more substituents independently selected from H, chloro, fluoro, bromo, hydroxy, methoxy, ethoxy, -O-CH₂-O-, trifluoromethoxy, 1-methylpiperidinylmethoxy, dimethylaminoethoxy, amino, dimethylamino, dimethylaminopropyl, diethylamino, aminosulfonyl, cyclohexyl, dimethylaminopropynyl, 3-(4-morpholinyl)propyn-1-yl, dimethylaminoethoxyethoxy, 3-(4-morpholinyl)propylamino, optionally substituted piperidinyl, morpholinyl, optionally substituted piperazinyl, optionally substituted phenyl, methyl, ethyl, propyl, cyano, hydroxymethyl, aminomethyl, nitro and trifluoromethyl;

provided R² is not 3-trifluoromethylphenyl when A³ is N, when A⁴ is CH, when n is 1, when R¹ is H and R⁸ is 4-hydroxy, 3-hydroxy or H; further provided R² is not 2-chloro-3-pyridyl when A³ is N, when A⁴ is CH, when n is 1, when R¹ is H and R⁸ is H or 4-methoxy; and further provided R² is not 2-methoxyphenyl when A³ is N, when A⁴ is CH, when n is 1, when R¹ is H and R⁸ is H.

The invention also relates to compounds of Formula III

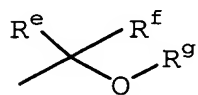


5 wherein R¹ is one or more substituents independently
selected from

- H,
- halo,
- hydroxy,
- 10 amino,
- C₁₋₆-alkyl,
- C₁₋₆-haloalkyl,
- C₁₋₆-alkoxy,
- C₁₋₂-alkylamino,
- 15 aminosulfonyl,
- C₃₋₆-cycloalkyl,
- cyano,
- oxo,
- C₁₋₂-hydroxyalkyl,
- 20 nitro,
- C₂₋₃-alkenyl,
- C₂₋₃-alkynyl,
- C₁₋₆-haloalkoxy,
- C₁₋₆-carboxyalkyl,
- 25 5-6-membered heterocyclyl-C₁₋₆-alkylamino,
- unsubstituted or substituted phenyl and
- unsubstituted or substituted 4-6 membered
- heterocyclyl,

preferably H, chloro, fluoro, bromo, amino, hydroxy,
methyl, ethyl, propyl, oxo, dimethylamino,
aminosulfonyl, cyclopropyl, cyano, hydroxymethyl,
nitro, propenyl, trifluoromethyl, methoxy, ethoxy,
5 trifluoromethoxy, carboxymethyl,
morpholinylethylamino, propynyl, unsubstituted or
substituted phenyl and unsubstituted or substituted
heteroaryl selected from thienyl,
furanyl, pyridyl, imidazolyl, and pyrazolyl,
10 more preferably H, chloro or fluoro;
wherein R² is selected from unsubstituted or substituted
phenyl, and
9-10 membered bicyclic and 13-14 membered tricyclic
unsaturated or partially unsaturated heterocyclyl,
15 preferably phenyl, 1,2-dihydroquinolyl, 1,2,3,4-
tetrahydro-isoquinolyl, 1,2,3,4-tetrahydro-quinolyl,
2,3-dihydro-1H-indolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-
aza-fluorenyl, 5,6,7-trihydro-1,2,4-triazolo[3,4-
a]isoquinolyl, 3,4-dihydro-2H-benzo[1,4]oxazinyl, and
20 benzo[1,4]dioxanyl,
more preferably phenyl, 1,2,3,4-tetrahydro-
isoquinolyl, 1,2,3,4-tetrahydro-quinolyl, 2,3-
dihydro-1H-indolyl and 3,4-dihydro-2H-
benzo[1,4]oxazinyl;
25 wherein substituted R² is substituted with one or more
substituents selected from halo, C₁₋₆-alkyl,
optionally substituted C₃₋₆-cycloalkyl, optionally
substituted phenyl, optionally substituted phenyl-
C₁-C₄-alkylenyl, C₁₋₂-haloalkoxy, optionally
30 substituted phenyloxy, optionally substituted 4-6
membered heterocyclyl-C₁-C₄-alkyl, optionally
substituted 4-6 membered heterocyclyl-C₂-C₄-alkenyl,
optionally substituted 4-6 membered heterocyclyl,
optionally substituted 4-6 membered

heterocycloxy, optionally substituted 4-6
 membered heterocyclyl-C₁-C₄-alkoxy, optionally
 substituted 4-6 membered heterocyclylsulfonyl,
 optionally substituted 4-6 membered
 5 heterocyclylamino, optionally substituted 4-6
 membered heterocyclylcarbonyl, optionally
 substituted 5-6 membered heterocyclylcarbonyl-C₁-4-
 alkyl, optionally substituted 4-6 membered
 heterocyclyl-C₁-4-alkylcarbonyl, C₁-2-haloalkyl, C₁-4-
 10 aminoalkyl, nitro, amino, hydroxy, cyano,
 aminosulfonyl, C₁-2-alkylsulfonyl, halosulfonyl, C₁-4-
 alkylcarbonyl, C₁-3-alkylamino-C₁-3-alkyl, C₁-3-
 alkylamino-C₁-3-alkoxy, C₁-3-alkylamino-C₁-3-alkoxy-C₁-
 3-alkoxy, C₁-4-alkoxycarbonyl, C₁-4-
 15 alkoxycarbonylamino-C₁-4-alkyl, C₁-4-hydroxyalkyl,



and C₁-4-alkoxy,

preferably bromo, chloro, fluoro, iodo, nitro, amino,
 cyano, aminoethyl, Boc-aminoethyl, hydroxy, oxo,
 aminosulfonyl, 4-methylpiperazinylsulfonyl,
 20 cyclohexyl, phenyl, phenylmethyl,
 morpholinylmethyl, 1-methylpiperazin-4-ylmethyl, 1-
 methylpiperazin-4-ylpropyl, morpholinylpropyl,
 piperidin-1-ylmethyl, 1-methylpiperidin-4-ylmethyl,
 2-methyl-2-(1-methylpiperidin-4-yl)ethyl,
 25 morpholinylethyl, 1-(4-morpholinyl)-2,2-
 dimethylpropyl, piperidin-4-ylethyl, 1-Boc-
 piperidin-4-ylethyl, piperidin-1-ylethyl, 1-Boc-
 piperidin-4-ylethyl, piperidin-4-ylmethyl, 1-Boc-
 piperidin-4-ylmethyl, piperidin-4-ylpropyl, 1-Boc-
 30 piperidin-4-ylpropyl, piperidin-1-ylpropyl,
 pyrrolidin-1-ylpropyl, pyrrolidin-2-ylpropyl, 1-
 Boc-pyrrolidin-2-ylpropyl, pyrrolidin-1-ylmethyl,
 pyrrolidin-2-ylmethyl, 1-Boc-pyrrolidin-2-ylmethyl,

pyrrolidinylpropenyl, pyrrolidinylbutenyl,
fluorosulfonyl, methylsulfonyl, methylcarbonyl,
Boc, piperidin-1-ylmethylcarbonyl, 4-
methylpiperazin-1-ylcarbonylethyl, methoxycarbonyl,
5 aminomethylcarbonyl, dimethylaminomethylcarbonyl,
3-ethoxycarbonyl-2-methyl-fur-5-yl, 4-
methylpiperazin-1-yl, 4-methyl-1-piperidyl, 1-Boc-
4-piperidyl, piperidin-4-yl, 1-methylpiperidin-4-
yl, 1-methyl-(1,2,3,6-tetrahydropyridyl),
10 imidazolyl, morpholinyl, 4-trifluoromethyl-1-
piperidinyl, hydroxybutyl, methyl, ethyl, propyl,
isopropyl, butyl, tert-butyl, sec-butyl,
trifluoromethyl, pentafluoroethyl, nonafluorobutyl,
dimethylaminopropyl, 1,1-di(trifluoromethyl)-1-
15 hydroxymethyl, 1,1-di(trifluoromethyl)-1-
(piperidinylethoxy)methyl, 1,1-di(trifluoromethyl)-
1-(methoxyethoxyethoxy)methyl, 1-hydroxyethyl, 2-
hydroxyethyl, trifluoromethoxy, 1-aminoethyl, 2-
aminoethyl, 1-(N-isopropylamino)ethyl, 2-(N-
20 isopropylamino)ethyl, dimethylaminoethoxy, 4-
chlorophenoxy, phenyloxy, azetidin-3-ylmethoxy, 1-
Boc-azetidin-3-ylmethoxy, pyrrol-2-ylmethoxy, 1-
Boc-pyrrol-2-ylmethoxy, pyrrol-1-ylmethoxy, 1-
methyl-pyrrol-2-ylmethoxy, 1-isopropyl-pyrrol-2-
25 ylmethoxy, 1-Boc-piperdin-4-ylmethoxy, piperdin-4-
ylmethoxy, 1-methylpiperdin-4-yloxy, isopropoxy,
methoxy and ethoxy,
more preferably bromo, chloro, fluoro,
morpholinylmethyl, 1-methylpiperazin-4-ylmethyl,
30 1-methylpiperazin-4-ylpropyl, morpholinylpropyl,
piperidin-1-ylmethyl, 1-methylpiperidin-4-
ylmethyl, 2-methyl-2-(1-methylpiperidin-4-
yl)ethyl, morpholinylethyl, 1-(4-morpholinyl)-
2,2-dimethylpropyl, piperidin-4-ylethyl, 1-Boc-

5 piperidin-4-ylethyl, piperidin-1-ylethyl, 1-Boc-
piperidin-4-ylethyl, piperidin-4-ylmethyl, 1-Boc-
piperidin-4-ylmethyl, piperidin-4-ylpropyl, 1-
Boc-piperidin-4-ylpropyl, piperidin-1-ylpropyl,
pyrrolidin-1-ylpropyl, pyrrolidin-2-ylpropyl, 1-
Boc-pyrrolidin-2-ylpropyl, pyrrolidin-1-ylmethyl,
pyrrolidin-2-ylmethyl, 1-Boc-pyrrolidin-2-
ylmethyl, 4-methylpiperazin-1-yl, 4-methyl-1-
10 piperidyl, 1-Boc-4-piperidyl, piperidin-4-yl, 1-
methyl-(1,2,3,6-tetrahydropyridyl), 1-methyl-
piperidin-4-yl, dimethylaminomethylcarbonyl,
aminomethylcarbonyl, methylcarbonyl, methyl,
ethyl, propyl, isopropyl, butyl, tert-butyl, sec-
butyl, trifluoromethyl, pentafluoroethyl,
15 dimethylaminopropyl, dimethylaminoethoxy, 4-
chlorophenoxy, phenyloxy, azetidin-3-ylmethoxy,
1-Boc-azetidin-3-ylmethoxy, pyrrol-1-ylethoxy, 1-
methyl-pyrrol-2-ylmethoxy, pyrrol-2-ylmethoxy, 1-
Boc-pyrrol-2-ylmethoxy, 1-Boc-piperdin-4-
20 ylmethoxy, piperdin-4-ylmethoxy, and 1-
methylpiperdin-4-yloxy,
particularly when R² is phenyl, it has a
substituent selected from optionally
substituted 4-6 membered heterocyclyl-C₁.C₄-
25 alkyl, optionally substituted 4-6 membered
heterocyclyl-C₂.C₄-alkenyl, optionally
substituted 4-6 membered heterocyclyl,
optionally substituted 4-6 membered
heterocycl-yloxy, optionally substituted 4-6
30 membered heterocyclyl-C₁.C₄-alkoxy, optionally
substituted 4-6 membered heterocyclylsulfonyl,
optionally substituted 4-6 membered
heterocyclylamino, optionally substituted 4-6
membered heterocyclylcarbonyl, optionally

substituted 4-6 membered heterocyclylcarbonyl-
C₁₋₄-alkyl, optionally substituted 4-6 membered
heterocyclyl-C₁₋₄-alkylcarbonyl;

wherein R⁷ is selected from H, C₁₋₃-alkyl, optionally

5 substituted phenyl-C₁₋₃-alkyl, 4-6 membered
heterocyclyl, and optionally substituted 4-6 membered
heterocyclyl-C₁₋₃-alkyl;

wherein R^e and R^f are independently selected from H and C₁₋₂-
haloalkyl,

10 preferably -CF₃;

wherein R^g is selected from H, C₁₋₃-alkyl, optionally
substituted phenyl-C₁₋₃-alkyl, 4-6 membered
heterocyclyl, and optionally substituted 4-6 membered
heterocyclyl-C₁₋₃-alkyl, C₁₋₃-alkoxy-C₁₋₂-alkyl and C₁₋₃-
15 alkoxy-C₁₋₃-alkoxy-C₁₋₃-alkyl; and

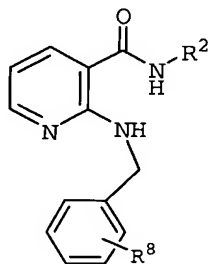
where R⁸ is one or more substituents selected from H, halo,
amino, hydroxy, C₁₋₆-alkyl, C₁₋₆-haloalkyl, C₁₋₆-alkoxy, C₁₋₆-
haloalkoxy, C₁₋₆-aminoalkyl, C₁₋₆-hydroxyalkyl,
optionally substituted phenyl, optionally substituted
20 heterocyclyl, optionally substituted heterocyclyl-C₁₋₆-
alkoxy, aminosulfonyl, C₃₋₆-cycloalkyl, C₁₋₆-alkylamino, C₁₋₆-
alkylamino-C₁₋₆-alkyl, optionally substituted
heterocyclyl-C₁₋₆-alkylamino, optionally substituted
heterocyclyl-C₁₋₆-alkyl, C₁₋₆-alkylamino-C₂₋₄-alkynyl, C₁₋₆-
25 alkylamino-C₁₋₆-alkoxy, C₁₋₆-alkylamino-C₁₋₆-alkoxy-C₁₋₆-
alkoxy, and optionally substituted heterocyclyl-C₂₋₄-
alkynyl,

preferably H, chloro, fluoro, bromo, hydroxy, methoxy,
ethoxy, -O-CH₂-O-, trifluoromethoxy, 1-
30 methylpiperidinylmethoxy, dimethylaminoethoxy,
amino, dimethylamino, dimethylaminopropyl,
diethylamino, aminosulfonyl, cyclohexyl,
dimethylaminopropynyl, 3-(4-morpholinyl)propyn-1-
yl, dimethylaminoethoxyethoxy, 3-(4-

morpholinyl)propylamino, optionally substituted
piperidinyl, morpholinyl, optionally substituted
piperazinyl, optionally substituted phenyl, methyl,
ethyl, propyl, cyano, hydroxymethyl, aminomethyl
5 and trifluoromethyl,
more preferably H, chloro, fluoro, bromo, cyano,
methoxy, -O-CH₂-O-, amino, trifluoromethyl,
trifluoromethoxy, 3-(4-morpholinyl)propyn-1-yl,
dimethylaminopropyl, and 3-(4-
10 morpholinyl)propylamino,
particularly 4-fluoro;
provided R² is not 3-trifluoromethylphenyl when R¹ is H and
R⁸ is 4-hydroxy, 3-hydroxy or H; and further provided R²
is not 2-methoxyphenyl when R¹ is H and R⁸ is H.

15

The invention also relates to compounds of Formula IV

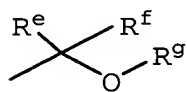
**IV**

20 wherein R² is selected from unsubstituted or substituted
phenyl, and
9-10 membered bicyclic and 11-14 membered tricyclic
unsaturated or partially unsaturated heterocyclyl,
preferably phenyl, 1,2-dihydroquinolyl, 1,2,3,4-
25 tetrahydro-isoquinolyl, 1',2'-dihydro-
spiro[cyclopropane-1,3'-[3H]indol]-6'-yl, isoquinolyl,
quinolyl, indolyl, isoindolyl, 2,3-dihydro-1H-indolyl,
naphthyridinyl, 1,2,3,4-tetrahydro-
[1,8]naphthyridinyl, quinoxalinyl,

benzo[d]isothiazolyl, 3,4-dihydro-quinazolinyl, 3,4-dihydro-2H-benzo[1,4]oxazinyl, 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinolyl, tetrahydroquinolinyl, indazolyl, 2,1,3-benzothiadiazolyl, benzodioxanyl, benzothienyl, benzofuryl, benzimidazolyl, dihydro-benzimidazolyl, benzoxazolyl and benzthiazolyl, more preferably 4,4-dimethyl-1,2,3,4-tetrahydro-1H-isoquinolinyl optionally substituted with Boc, 4,4-dimethyl-1,2,3,4-tetrahydro-quinolyl optionally substituted with one or more substituents selected from Boc and oxo, 3,3-dimethyl-2,3-dihydro-1H-indolyl optionally substituted with one or more substituents selected from methylsulfonyl, 1-Boc-piperidin-4-ylmethyl, piperidin-4-ylmethyl, 1-Boc-piperidin-4-yl, piperidin-4-yl, 1-methyl-piperidin-4-ylmethyl, 1-methyl-piperidin-4-yl, pyrrolidin-1-yl-carbonyl, dimethylaminomethylcarbonyl, aminomethylcarbonyl, methylcarbonyl, pyrrolidin-2-ylmethyl, and 1-Boc-pyrrolidin-2-ylmethyl, and 3,4-dihydro-2H-benzo[1,4]oxazinyl optionally substituted with one or more substituents selected from methyl, and methylcarbonyl; and particularly 3,3-dimethyl-2,3-dihydro-1H-indolyl optionally substituted with a substituent selected from pyrrolidin-1-yl-carbonyl, methylcarbonyl, and methylsulfonyl, and 4,4-dimethyl-1,2,3,4-tetrahydro-1H-isoquinolinyl;

wherein substituted R² is substituted with one or more substituents selected from halo, C₁₋₆-alkyl,

optionally substituted C₃₋₆-cycloalkyl, optionally
 substituted phenyl, optionally substituted phenyl-
 C₁-C₄-alkylenyl, C₁₋₂-haloalkoxy, optionally
 substituted phenyloxy, optionally substituted 4-6
 5 membered heterocyclyl-C₁-C₆-alkyl, optionally
 substituted 4-6 membered heterocyclyl-C₂-C₄-alkenyl,
 optionally substituted 4-6 membered heterocyclyl,
 optionally substituted 4-6 membered
 heterocyclyloxy, optionally substituted 4-6
 10 membered heterocyclyl-C₁₋₄-alkoxy, optionally
 substituted 4-6 membered heterocyclylsulfonyl,
 optionally substituted 4-6 membered
 heterocyclylamino, optionally substituted 4-6
 membered heterocyclylcarbonyl, optionally
 15 substituted 4-6 membered heterocyclyl-C₁₋₄-
 alkylcarbonyl, optionally substituted 4-6 membered
 heterocyclylcarbonyl-C₁₋₄-alkyl, optionally
 substituted 4-6 membered heterocyclyl-C₁₋₄-
 alkylcarbonylamino, optionally substituted 4-6
 20 membered heterocyclyl-oxycarbonylamino, C₁₋₂-
 haloalkyl, C₁₋₄-aminoalkyl, nitro, amino, C₁₋₃-
 alkylsulfonylamino, hydroxy, cyano, aminosulfonyl,
 C₁₋₂-alkylsulfonyl, halosulfonyl, C₁₋₄-alkylcarbonyl,
 amino-C₁₋₄-alkylcarbonyl, C₁₋₃-alkylamino-C₁₋₄-
 25 alkylcarbonyl, C₁₋₃-alkylamino-C₁₋₄-
 alkylcarbonylamino, C₁₋₄-alkoxycarbonyl-C₁₋₄-alkyl,
 C₁₋₃-alkylamino-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkoxy,
 C₁₋₃-alkylamino-C₁₋₃-alkoxy-C₁₋₃-alkoxy, C₁₋₄-
 alkoxycarbonyl, C₁₋₄-alkoxycarbonylamino-C₁₋₄-alkyl,
 30 C₁₋₃-alkylsulfonylamino-C₁₋₃-alkoxy, C₁₋₄-hydroxyalkyl,



and C₁₋₄-alkoxy,
 preferably bromo, chloro, fluoro, iodo, nitro, amino,
 cyano, Boc-aminoethyl, hydroxy, oxo,

fluorosulfonyl, methylsulfonyl, aminosulfonyl, 4-methylpiperazinylsulfonyl, cyclohexyl, phenyl, phenylmethyl, 4-pyridylmethyl, 4-morpholinylmethyl, 1-methylpiperazin-4-ylmethyl, 1-methylpiperazin-4-ylpropyl, morpholinylpropyl, piperidin-1-ylmethyl, 1-methylpiperidin-4-ylmethyl, 2-methyl-2-(1-methylpiperidin-4-yl)ethyl, 2-methyl-2-(4-pyrimidinyl)ethyl, 2-methyl-2-(5-methyloxadiazol-2-yl)ethyl, 2-methyl-2-(pyrazol-5-yl)ethyl, 2-methyl-2-(1-ethoxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)ethyl, morpholinylethyl, 1-(4-morpholinyl)-2,2-dimethylpropyl, 1-(4-morpholinyl)-2,2-dimethylethyl, piperidin-4-ylethyl, 1-Boc-piperidin-4-ylethyl, piperidin-1-ylethyl, 1-Boc-piperidin-4-ylethyl, piperidin-4-ylmethyl, 1-Boc-piperidin-4-ylmethyl, piperidin-4-ylpropyl, 1-Boc-piperidin-4-ylpropyl, piperidin-1-ylpropyl, pyrrolidin-1-ylpropyl, pyrrolidin-2-ylpropyl, 1-Boc-pyrrolidin-2-ylpropyl, 1-(pyrrolidin-1-yl)-2-methylpropyl, pyrrolidin-1-ylmethyl, pyrrolidin-2-ylmethyl, 1-Boc-pyrrolidin-2-ylmethyl, 2-methyl-2-(pyrrolidin-1-yl)ethyl, pyrrolidinylpropenyl, pyrrolidinylbutenyl, methylcarbonyl, Boc, piperidin-1-ylmethylcarbonyl, pyrrolidin-1-yl-carbonyl, pyrrolidin-2-yl-carbonyl, 4-pyridylcarbonyl, 4-methylpiperazin-1-ylcarbonylethyl, $\text{CH}_3\text{O}-\text{C}(=\text{O})-\text{CH}_2-$, methoxycarbonyl, aminomethylcarbonyl, dimethylaminomethylcarbonyl, methylsulfonylamino, dimethylaminomethylcarbonylamino, 1-pyrrolidinyl- $\text{CH}_2-\text{C}(=\text{O})-\text{NH}-$, 4-morpholinyl- $\text{CH}_2-\text{C}(=\text{O})-\text{NH}-$, 3-tetrahydrofuryl- $\text{O}-\text{C}(=\text{O})-\text{NH}-$, cyclohexyl- $\text{N}(\text{CH}_3)-$, (4-pyrimidinyl)amino, (2-methylthio-4-pyrimidinyl)amino, 3-ethoxycarbonyl-2-methyl-fur-5-

yl, 4-methylpiperazin-1-yl, 4-methyl-1-piperidyl,
1-Boc-4-piperidyl, piperidin-4-yl, 1-
methylpiperidin-4-yl, 1-methyl-(1,2,3,6-
5 tetrahydropyridyl), imidazolyl, morpholinyl, 4-
trifluoromethyl-1-piperidinyl, hydroxybutyl,
methyl, ethyl, propyl, isopropyl, butyl, tert-
butyl, sec-butyl, trifluoromethyl,
pentafluoroethyl, nonafluorobutyl,
dimethylaminopropyl, 1,1-di(trifluoromethyl)-1-
10 hydroxymethyl, 1,1-di(trifluoromethyl)-1-
(piperidinylethoxy)methyl, 1,1-di(trifluoromethyl)-
1-(pyrrolidin-2-ylmethoxy)methyl, 1,1-
di(trifluoromethyl)-1-(methoxyethoxyethoxy)methyl,
1-hydroxyethyl, 2-hydroxyethyl, trifluoromethoxy,
15 1-aminoethyl, 2-aminoethyl, 1-(N-
isopropylamino)ethyl, 2-(N-isopropylamino)ethyl, 3-
tetrahydrofuryloxy, dimethylaminoethoxy, 4-
chlorophenoxy, phenyloxy, azetidin-3-ylmethoxy, 1-
Boc-azetidin-3-ylmethoxy, 3-tetrahydrofurylmethoxy,
20 pyrrolidin-2-ylmethoxy, 1-methylcarbonyl-
pyrrolidin-2-ylmethoxy, 1-Boc-pyrrolidin-2-
ylmethoxy, pyrrolidin-1-ylmethoxy, 1-methyl-
pyrrolidin-2-ylmethoxy, 1-isopropyl-pyrrolidin-2-
ylmethoxy, 1-Boc-piperdin-4-ylmethoxy, (1-
25 pyrrolidinyl)ethoxy, piperdin-4-ylmethoxy,
piperdin-3-ylmethoxy, 1-methylpiperdin-4-yloxy,
methylsulfonylaminoethoxy, isopropoxy, methoxy and
ethoxy,
more preferably bromo, chloro, fluoro,
30 morpholinylmethyl, 1-methylpiperazin-4-ylmethyl,
1-methylpiperazin-4-ylpropyl, morpholinylpropyl,
piperidin-1-ylmethyl, 1-methylpiperidin-4-
ylmethyl, 2-methyl-2-(1-methylpiperidin-4-
yl)ethyl, morpholinylethyl, 1-(4-morpholinyl)-

2,2-dimethylpropyl, piperidin-4-ylethyl, 1-Boc-piperidin-4-ylethyl, piperidin-1-ylethyl, 1-Boc-piperidin-4-ylethyl, piperidin-4-ylmethyl, 1-Boc-piperidin-4-ylmethyl, piperidin-4-ylpropyl, 1-Boc-piperidin-4-ylpropyl, piperidin-1-ylpropyl, pyrrolidin-1-ylpropyl, pyrrolidin-2-ylpropyl, 1-Boc-pyrrolidin-2-ylpropyl, pyrrolidin-1-ylmethyl, pyrrolidin-2-ylmethyl, 1-Boc-pyrrolidin-2-ylmethyl, 4-methylpiperazin-1-yl, 4-methyl-1-piperidyl, 1-Boc-4-piperidyl, piperidin-4-yl, 1-methyl-(1,2,3,6-tetrahydropyridyl), 1-methylpiperidin-4-yl, dimethylaminomethylcarbonyl, aminomethylcarbonyl, methylcarbonyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, sec-butyl, trifluoromethyl, pentafluoroethyl, dimethylaminopropyl, dimethylaminoethoxy, 4-chlorophenoxy, phenyloxy, azetidin-3-ylmethoxy, 1-Boc-azetidin-3-ylmethoxy, pyrrol-1-ylethoxy, 1-methyl-pyrrol-2-ylmethoxy, pyrrol-2-ylmethoxy, 1-Boc-pyrrol-2-ylmethoxy, 1-Boc-piperdin-4-ylmethoxy, piperdin-4-ylmethoxy, and 1-methylpiperdin-4-yloxy, particularly when R² is phenyl, it has a substituent selected from chloro, tert-butyl, azetidin-3-ylmethoxy, 1-Boc-azetidin-3-ylmethoxy, dimethylaminomethylcarbonylamino, 1,1-di(trifluoromethyl)-1-(pyrrolidin-2-ylmethoxy)methyl, trifluoromethyl, 2-methyl-2-(morpholin-4-yl)ethyl, 2-methyl-2-(pyrrolidin-1-yl)ethyl, 2-methyl-2-(5-methyloxadiazol-2-yl)ethyl, methylsulfonylamino, 1-methylpyrrolidin-2-ylmethoxy, and isopropyl; more particularly 3-trifluorophenyl meta-substituted with a substituent selected from

azetidin-3-ylmethoxy, 1-Boc-azetidin-3-ylmethoxy, methylsulfonylamino and 1-methylpyrrolidin-2-ylmethoxy;

wherein R^e and R^f are independently selected from H and C₁₋₂-

5 haloalkyl,
preferably trifluoromethyl;

wherein R^g is selected from H, C₁₋₃-alkyl, optionally

substituted phenyl-C₁₋₃-alkyl, 4-6 membered
heterocyclyl, and optionally substituted 4-6 membered
10 heterocyclyl-C₁₋₃-alkyl, C₁₋₃-alkoxy-C₁₋₂-alkyl and C₁₋₃-
alkoxy-C₁₋₃-alkoxy-C₁₋₃-alkyl; and

where R^h is one or more substituents selected from halo,

amino, nitro, hydroxy, C₁₋₆-alkyl, C₁₋₆-haloalkyl, C₁₋₆-
alkoxy, C₁₋₆-haloalkoxy, C₁₋₆-aminoalkyl, C₁₋₆-hydroxyalkyl,
15 optionally substituted phenyl, optionally substituted
heterocyclyl, optionally substituted heterocyclyl-C₁₋₆-
alkoxy, aminosulfonyl, C₃₋₆-cycloalkyl, C₁₋₆-alkylamino, C₁₋₆-
alkylamino-C₁₋₆-alkyl, optionally substituted
heterocyclyl-C₁₋₆-alkylamino, optionally substituted
20 heterocyclyl-C₁₋₆-alkyl, C₁₋₆-alkylamino-C₂₋₄-alkynyl, C₁₋₆-
alkylamino-C₁₋₆-alkoxy, C₁₋₆-alkylamino-C₁₋₆-alkoxy-C₁₋₆-
alkoxy, and optionally substituted heterocyclyl-C₂₋₄-
alkynyl,

preferably chloro, fluoro, bromo, hydroxy, methoxy,
25 ethoxy, -O-CH₂-O-, trifluoromethoxy, 1-
methylpiperidinylmethoxy, dimethylaminoethoxy,
amino, dimethylamino, dimethylaminopropyl,
diethylamino, aminosulfonyl, cyclohexyl,
dimethylaminopropynyl, 3-(4-morpholinyl)propyn-1-
30 yl, dimethylaminoethoxyethoxy, 3-(4-
morpholinyl)propylamino, optionally substituted
piperidinyl, morpholinyl, optionally substituted
piperazinyl, optionally substituted phenyl, methyl,

ethyl, propyl, cyano, hydroxymethyl, aminomethyl
and trifluoromethyl,
more preferably fluoro, hydroxy, amino, and nitro,
and particularly 4-fluoro;
5 provided R² is not 3-trifluoromethylphenyl when R⁸ is 4-
hydroxy, or 3-hydroxy.

A family of specific compounds of particular interest
within Formula I consists of compounds and pharmaceutically-
10 acceptable derivatives thereof as follows:

2-(3-Fluoro-benzylamino)-N-(4-phenoxy-phenyl)-nicotinamide;
2-(3-Fluoro-benzylamino)-N-(4-phenoxy-phenyl)-nicotinamide,
trifluoroacetate salt;
15 N-[4-tert-Butyl-3-(pyrrolidin-2-ylmethoxy)-phenyl]-2-(4-
fluoro-benzylamino)-nicotinamide, hydrochloride salt;
N-(4-Phenoxy-phenyl)-2-(3-trifluoromethyl-benzylamino)-
nicotinamide;
2-(4-Fluoro-benzylamino)-N-(4-phenoxy-phenyl)-nicotinamide;
20 N-(4-Phenoxy-phenyl)-2-(4-trifluoromethyl-benzylamino)-
nicotinamide;
2-(2-Bromo-benzylamino)-N-(4-phenoxy-phenyl)-nicotinamide;
N-(4-Phenoxy-phenyl)-2-(4-trifluoromethoxy-benzylamino)-
nicotinamide;
25 2-(2,3-Difluoro-benzylamino)-N-(4-phenoxy-phenyl)-
nicotinamide;
N-(4-Chlorophenyl)-2-([(4-cyanophenyl)methyl]amino)(3-
pyridyl)carboxamide;
N-(4-Chlorophenyl)-2-([(2-cyanophenyl)methyl]amino)(3-
30 pyridyl)carboxamide;
N-(4-sec-butylphenyl)-2-[(4-fluorobenzyl)amino]nicotinamide;
N-(4-tert-Butylphenyl)-2-[(4-
fluorobenzyl)amino]nicotinamide;

N-(4-Isopropyl-phenyl)-2-(3-methoxy-benzylamino)-
nicotinamide;

(2-[[(3-Aminophenyl)methyl]amino] (3-pyridyl)) -N-[4-
(methylethyl)phenyl]carboxamide;

5 (2-[[(4-Fluorophenyl)methyl]amino] (3-pyridyl)) -N-[4-
(methylethyl)phenyl]carboxamide;

(2-[[(4-Fluorophenyl)methyl]amino] (3-pyridyl)) -N-[3-
(trifluoromethyl)phenyl]carboxamide;

10 (2-[[(3,4-Dimethoxyphenyl)methyl]amino] (3-pyridyl)) -N-[3-
(trifluoromethyl)phenyl]carboxamide;

{2-[Benzylamino] (3-pyridyl)) -N-[3-(trifluoromethyl)
phenyl]-carboxamide;

(2-[[(3-Chlorophenyl)methyl]amino] (3-pyridyl)) -N-[3-
(trifluoromethyl)phenyl]carboxamide;

15 (2-[[(4-Bromophenyl)methyl]amino] (3-pyridyl)) -N-[3-
(trifluoromethyl)phenyl]carboxamide;

(2-[[(4-Chlorophenyl)methyl]amino] (3-pyridyl)) -N-[3-
(trifluoromethyl)phenyl]carboxamide;

20 (2-[[(2,4-Difluorophenyl)methyl]amino] (3-pyridyl)) -N-[3-
(trifluoromethyl)phenyl]carboxamide;

(2-[[(4-Fluorophenyl)ethyl]amino] (3-pyridyl)) -N-[3-
(trifluoromethyl)phenyl]carboxamide;

(2-[[(3,4-Difluorophenyl)methyl]amino] (3-pyridyl)) -N-[3-
(trifluoromethyl)phenyl]carboxamide;

25 (2-[[(2,3-Difluorophenyl)methyl]amino] (3-pyridyl)) -N-[3-
(trifluoromethyl)phenyl]carboxamide;

(2-[[(2-Fluorophenyl)methyl]amino] (3-pyridyl)) -N-[3-
(trifluoromethyl)phenyl]carboxamide;

30 (2-[[(2,6-Difluorophenyl)methyl]amino] (3-pyridyl)) -N-[3-
(trifluoromethyl)phenyl]carboxamide;

(2-[[(3-Bromophenyl)methyl]amino] (3-pyridyl)) -N-[3-
(trifluoromethyl)phenyl]carboxamide;

(2-[[(4-Fluorophenyl)methyl]amino] (3-pyridyl)) -N-[4-
(trifluoromethyl)phenyl]carboxamide;

N-{3-[3-(Dimethylamino)propyl]-5-(trifluoromethyl)phenyl}(2-
{[(4-fluorophenyl)methyl]amino}(3-pyridyl))carboxamide;
{2-[(3-[3-(Dimethylamino)propyl]-4-
fluorophenyl)methyl]amino}(3-pyridyl))-N-[4-(tert-
5 butyl)phenyl]carboxamide;
{2-[(3-[3-(Dimethylamino)propyl]-4-
fluorophenyl)methyl]amino}(3-pyridyl))-N-[4-
(trifluoromethyl)phenyl]carboxamide;
{2-[(3-[3-(Dimethylamino)propyl]-4-
10 fluorophenyl)methyl]amino}(3-pyridyl))-N-(4-bromo-2-
fluorophenyl)carboxamide;
2-[4-Fluorobenzyl]amino)-N-[4-tert-butyl-3-(1,2,3,6-
tetrahydropyridin-4-yl)phenyl]nicotinamide; and
{2-[(4-Fluoro-3-(3-morpholin-4-ylprop-1-
15 ynyl)phenyl)methyl]amino}(3-pyridyl))-N-[3-
(trifluoromethyl)phenyl]carboxamide.

Another family of specific compounds of particular
interest within Formula I consists of compounds and
20 pharmaceutically-acceptable derivatives thereof as follows:

N-(3,3-Dimethyl-1-(methanesulfonyl)-2,3-dihydro-1H-indol-6-
yl)-2-((4-fluorophenyl)methyl)amino)-3-
pyridinecarboxamide;
25 N-(4-(1,1-dimethylethyl)-3-((N,N-
dimethylglycyl)amino)phenyl)-2-((4-
fluorophenyl)methyl)amino)-3-pyridinecarboxamide;
N-(3-(((2R)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-
(trifluoromethyl)phenyl)-2-((3-(1,3-oxazol-5-
30 yl)phenyl)amino)-3-pyridinecarboxamide;
2-((4-fluorophenyl)methyl)amino)-N-(3-(((2R)-1-methyl-2-
pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-3-
pyridinecarboxamide;

- 2-(((4-fluorophenyl)methyl)amino)-N-(3-
((methylsulfonyl)amino)-5-(trifluoromethyl)phenyl)-3-
pyridinecarboxamide;
- 2-((3-(1,3-oxazol-5-yl)phenyl)amino)-N-(3-
5 (trifluoromethyl)phenyl)-3-pyridinecarboxamide;
- 2-(((4-fluorophenyl)methyl)amino)-N-(4-(1-methyl-1-(5-
methyl-1,3,4-oxadiazol-2-yl)ethyl)phenyl)-3-
pyridinecarboxamide;
- 3-(2-Chloro-5-{[2-(4-fluoro-benzylamino)-pyridine-3-
10 carbonyl]-amino}-phenoxy-methyl)-azetidine-1-carboxylic
acid tert-butyl ester;
- N-[3-(Azetidin-3-ylmethoxy)-4-chloro-phenyl]-2-(4-fluoro-
benzylamino)-nicotinamide;
- 6-Chloro-3-(4-fluoro-benzylamino)-pyridazine-4-carboxylic
15 acid (4-tert-butyl-phenyl)-amide;
- 3-(4-Fluoro-benzylamino)-pyridazine-4-carboxylic acid (4-
tert-butyl-phenyl)-amide;
- 2-(4-Hydroxy-3-amino-benzylamino)-N-(4-isopropyl-phenyl)-
nicotinamide ;
- 20 2-(4-Hydroxy-3-nitro-benzylamino)-N-(4-isopropyl-phenyl)-
nicotinamide;
- 3-(4-Fluoro-benzylamino)-1,2,5,6-tetrahydro-pyridazine-4-
carboxylic acid (4-tert-butyl-phenyl)-amide; and
- N-[3-(Azetidin-3-ylmethoxy)-5-trifluoromethyl-phenyl]-2-(4-
25 fluoro-benzylamino)-nicotinamide.

Indications

Compounds of the present invention would be useful
for, but not limited to, the prevention or treatment of
30 angiogenesis-related diseases. The compounds of the
invention have kinase inhibitory activity, such as VEGFR/KDR
inhibitory activity. The compounds of the invention are
useful in therapy as antineoplasia agents or to minimize
deleterious effects of VEGF.

Compounds of the invention would be useful for the treatment of neoplasia including cancer and metastasis, including, but not limited to: carcinoma such as cancer of the bladder, breast, colon, kidney, liver, lung (including small cell lung cancer), esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin (including squamous cell carcinoma); hematopoietic tumors of lymphoid lineage (including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma); hematopoietic tumors of myeloid lineage (including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia); tumors of mesenchymal origin (including fibrosarcoma and rhabdomyosarcoma, and other sarcomas, e.g. soft tissue and bone); tumors of the central and peripheral nervous system (including astrocytoma, neuroblastoma, glioma and schwannomas); and other tumors (including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderma pigmentosum, keratocanthoma, thyroid follicular cancer and Kaposi's sarcoma).

Preferably, the compounds are useful for the treatment of neoplasia selected from lung cancer, colon cancer and breast cancer.

The compounds also would be useful for treatment of ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, retrolental fibroplasia and neovascular glaucoma; retinal ischemia; vitreous hemorrhage; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemangiomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female

reproductive system such as endometriosis. The compounds are also useful for the treatment of edema, and conditions of vascular hyperpermeability.

The compounds of the invention are useful in therapy
5 of proliferative diseases. These compounds can be used for the treatment of an inflammatory rheumatoid or rheumatic disease, especially of manifestations at the locomotor apparatus, such as various inflammatory rheumatoid diseases, especially chronic polyarthritis including rheumatoid
10 arthritis, juvenile arthritis or psoriasis arthropathy; paraneoplastic syndrome or tumor-induced inflammatory diseases, turbid effusions, collagenosis, such as systemic Lupus erythematosus, poly-myositis, dermato-myositis, systemic sclerodermia or mixed collagenosis; postinfectious
15 arthritis (where no living pathogenic organism can be found at or in the affected part of the body), seronegative spondylarthritis, such as spondylitis ankylosans; vasculitis, sarcoidosis, or arthrosis; or further any combinations thereof. An example of an inflammation related
20 disorder is (a) synovial inflammation, for example, synovitis, including any of the particular forms of synovitis, in particular bursal synovitis and purulent synovitis, as far as it is not crystal-induced. Such synovial inflammation may for example, be consequential to
25 or associated with disease, e.g. arthritis, e.g. osteoarthritis, rheumatoid arthritis or arthritis deformans. The present invention is further applicable to the systemic treatment of inflammation, e.g. inflammatory diseases or conditions, of the joints or locomotor apparatus in the
30 region of the tendon insertions and tendon sheaths. Such inflammation may be, for example, be consequential to or associated with disease or further (in a broader sense of the invention) with surgical intervention, including, in particular conditions such as insertion endopathy,

myofasciale syndrome and tendomyosis. The present invention is further especially applicable to the treatment of inflammation, e.g. inflammatory disease or condition, of connective tissues including dermatomyositis and myositis.

5 These compounds can be used as active agents against such disease states as arthritis, atherosclerosis, psoriasis, hemangiomas, myocardial angiogenesis, coronary and cerebral collaterals, ischemic limb angiogenesis, wound healing, peptic ulcer Helicobacter related diseases,
10 fractures, cat scratch fever, rubeosis, neovascular glaucoma and retinopathies such as those associated with diabetic retinopathy or macular degeneration. In addition, some of these compounds can be used as active agents against solid tumors, malignant ascites, hematopoietic cancers and
15 hyperproliferative disorders such as thyroid hyperplasia (especially Grave's disease), and cysts (such as hypervascularity of ovarian stroma, characteristic of polycystic ovarian syndrome (Stein- Leventhal syndrome)) since such diseases require a proliferation of blood vessel
20 cells for growth and/or metastasis.

 Further, some of these compounds can be used as active agents against burns, chronic lung disease, stroke, polyps, anaphylaxis, chronic and allergic inflammation, ovarian hyperstimulation syndrome, brain tumor-associated cerebral
25 edema, high-altitude, trauma or hypoxia induced cerebral or pulmonary edema, ocular and macular edema, ascites, and other diseases where vascular hyperpermeability, effusions, exudates, protein extravasation, or edema is a manifestation of the disease. The compounds will also be useful in
30 treating disorders in which protein extravasation leads to the deposition of fibrin and extracellular matrix, promoting stromal proliferation (e.g. fibrosis, cirrhosis and carpal tunnel syndrome).

The compounds of the present invention are also useful in the treatment of ulcers including bacterial, fungal, Mooren ulcers and ulcerative colitis.

5 The compounds of the present invention are also useful in the treatment of conditions wherein undesired angiogenesis, edema, or stromal deposition occurs in viral infections such as Herpes simplex, Herpes Zoster, AIDS, Kaposi's sarcoma, protozoan infections and toxoplasmosis, following trauma, radiation, stroke, endometriosis, ovarian
10 hyperstimulation syndrome, systemic lupus, sarcoidosis, synovitis, Crohn's disease, sickle cell anaemia, Lyme disease, pemphigoid, Paget's disease, hyperviscosity syndrome, Osler-Weber-Rendu disease, chronic inflammation, chronic occlusive pulmonary disease, asthma, and
15 inflammatory rheumatoid or rheumatic disease. The compounds are also useful in the reduction of sub-cutaneous fat and for the treatment of obesity.

The compounds of the present invention are also useful in the treatment of ocular conditions such as ocular and
20 macular edema, glaucoma, ocular neovascular disease, scleritis, radial keratotomy, uveitis, vitritis, myopia, optic pits, chronic retinal detachment, post-laser complications, conjunctivitis, Stargardt's disease and Eales disease in addition to retinopathy and macular degeneration.

25 The compounds of the present invention are also useful in the treatment of cardiovascular conditions such as atherosclerosis, restenosis, arteriosclerosis, vascular occlusion and carotid obstructive disease.

The compounds of the present invention are also useful
30 in the treatment of cancer related indications such as solid tumors, sarcomas (especially Ewing's sarcoma and osteosarcoma), retinoblastoma, rhabdomyosarcomas, neuroblastoma, hematopoietic malignancies, including

leukemia and lymphoma, tumor- induced pleural or pericardial effusions, and malignant ascites.

The compounds of the present invention are also useful in the treatment of diabetic conditions such as diabetic
5 retinopathy and microangiopathy.

The compounds of this invention may also act as inhibitors of other protein kinases, e.g. p38, EGFR, CDK-2, CDK-5, IKK, JNK3, bFGFR, PDGFR and RAF and thus be effective in the treatment of diseases associated with other protein
10 kinases.

Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred
15 animals include horses, dogs, and cats.

As used herein, the compounds of the present invention include the pharmaceutically acceptable derivatives thereof.

20 **Definitions**

A "pharmaceutically-acceptable derivative" denotes any salt, ester of a compound of this invention, or any other compound which upon administration to a patient is capable of providing (directly or indirectly) a compound of this
25 invention, or a metabolite or residue thereof, characterized by the ability to inhibit angiogenesis.

The term "treatment" includes therapeutic treatment as well as prophylactic treatment (either preventing the onset of disorders altogether or delaying the onset of a
30 preclinically evident stage of disorders in individuals).

The phrase "therapeutically-effective" is intended to qualify the amount of each agent, which will achieve the goal of improvement in disorder severity and the frequency of incidence over treatment of each agent by itself, while

avoiding adverse side effects typically associated with alternative therapies. For example, effective neoplastic therapeutic agents prolong the survivability of the patient, inhibit the rapidly-proliferating cell growth associated
5 with the neoplasm, or effect a regression of the neoplasm.

The term "prevention" includes either preventing the onset of disorders altogether or delaying the onset of a preclinically evident stage of disorders in individuals. This includes prophylactic treatment of those at risk of
10 developing a disease, such as a cancer, for example. "Prophylaxis" is another term for prevention.

The term "H" denotes a single hydrogen atom. This radical may be attached, for example, to an oxygen atom to form a hydroxyl radical.

15 Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylamino", it embraces linear or branched radicals having one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about six carbon atoms.
20 Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl and the like. Even more preferred are lower alkyl radicals having one or two carbon atoms. The term "alkylenyl" embraces bridging divalent alkyl radicals such
25 as methylenyl and ethylenyl. The term "lower alkyl substituted with R¹" does not include an acetal moiety.

The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twelve carbon atoms. More preferred alkenyl
30 radicals are "lower alkenyl" radicals having two to about six carbon atoms. Most preferred lower alkenyl radicals are radicals having two to about four carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower

alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "alkynyl" denotes linear or branched radicals having at least one carbon-carbon triple bond and having two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about six carbon atoms. Most preferred are lower alkynyl radicals having two to about four carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals including perhaloalkyl. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Even more preferred are lower haloalkyl radicals having one to three carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Perfluoroalkyl" means alkyl radicals having all hydrogen atoms replaced with fluoro atoms. Examples include trifluoromethyl and pentafluoroethyl.

The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower

hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. Even more preferred are lower
5 hydroxyalkyl radicals having one to three carbon atoms.

The term "alkoxy" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms.
10 Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy. Even more preferred are lower alkoxy radicals having one to three carbon atoms. Alkoxy radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy"
15 radicals. Even more preferred are lower haloalkoxy radicals having one to three carbon atoms. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

The term "aryl", alone or in combination, means a
20 carbocyclic aromatic system containing one or two rings wherein such rings may be attached together in a fused manner. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, indenyl, tetrahydronaphthyl, and indanyl. More preferred aryl is phenyl. Said "aryl" group may have 1
25 to 3 substituents such as lower alkyl, hydroxyl, halo, haloalkyl, nitro, cyano, alkoxy and lower alkylamino. Phenyl substituted with -O-CH₂-O- forms the aryl benzodioxolyl substituent.

The term "heterocyclyl" embraces saturated, partially
30 saturated and unsaturated heteroatom-containing ring radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. It does not include rings containing -O-O-, -O-S- or -S-S- portions. Said "heterocyclyl" group may have 1 to 3 substituents such as

hydroxyl, Boc, halo, haloalkyl, cyano, lower alkyl, lower aralkyl, oxo, lower alkoxy, amino and lower alkylamino.

Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, piperazinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl]. Examples of partially saturated heterocyclic radicals include dihydrothienyl, dihydropyranyl, dihydrofuryl and dihydrothiazolyl.

Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals, include unsaturated 5 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl]; unsaturated 5- to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl].

The term also embraces radicals where heterocyclic radicals are fused/condensed with aryl radicals:

unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indoliziny, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g.,
5 tetrazolo [1,5-b]pyridazinyl]; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl]; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g.,
10 benzothiazolyl, benzothiadiazolyl]; and saturated, partially unsaturated and unsaturated condensed heterocyclic group containing 1 to 2 oxygen or sulfur atoms [e.g. benzofuryl, benzothienyl, 2,3-dihydro-benzo[1,4]dioxinyl and dihydrobenzofuryl]. Preferred heterocyclic radicals include
15 five to ten membered fused or unfused radicals. More preferred examples of heteroaryl radicals include quinolyl, isoquinolyl, imidazolyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, and pyrazinyl. Other preferred heteroaryl radicals are 5- or 6-membered heteroaryl, containing one or
20 two heteroatoms selected from sulfur, nitrogen and oxygen, selected from thienyl, furyl, pyrrolyl, indazolyl, pyrazolyl, oxazolyl, triazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, piperidinyl and pyrazinyl.

25 Particular examples of non-nitrogen containing heteroaryl include pyranyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, benzofuryl, benzothienyl, and the like.

 Particular examples of partially saturated and saturated heterocyclyl include pyrrolidinyl, imidazolidinyl,
30 piperidinyl, pyrrolinyl, pyrazolidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, thiazolidinyl, dihydrothienyl, 2,3-dihydro-benzo[1,4]dioxanyl, indolinyl, isoindolinyl, dihydrobenzothienyl, dihydrobenzofuryl, isochromanyl, chromanyl, 1,2-dihydroquinolyl, 1,2,3,4-

tetrahydro-isoquinolyl, 1,2,3,4-tetrahydro-quinolyl,
2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-
1,2,4-triazolo[3,4-a]isoquinolyl, 3,4-dihydro-2H-
benzo[1,4]oxazinyl, benzo[1,4]dioxanyl, 2,3-dihydro-1H-1λ'-
5 benzo[d]isothiazol-6-yl, dihydropyranyl, dihydrofuryl and
dihydrothiazolyl, and the like.

The term "sulfonyl", whether used alone or linked to
other terms such as alkylsulfonyl, denotes respectively
divalent radicals $\text{-SO}_2\text{-}$.

10 The terms "sulfamyl," "aminosulfonyl" and
"sulfonamidyl," denotes a sulfonyl radical substituted with
an amine radical, forming a sulfonamide ($\text{-SO}_2\text{NH}_2$).

The term "alkylaminosulfonyl" includes "N-
alkylaminosulfonyl" where sulfamyl radicals are
15 independently substituted with one or two alkyl radical(s).
More preferred alkylaminosulfonyl radicals are "lower
alkylaminosulfonyl" radicals having one to six carbon atoms.
Even more preferred are lower alkylaminosulfonyl radicals
having one to three carbon atoms. Examples of such lower
20 alkylaminosulfonyl radicals include N-methylaminosulfonyl,
and N-ethylaminosulfonyl.

The terms "carboxy" or "carboxyl", whether used alone
or with other terms, such as "carboxyalkyl", denotes $\text{-CO}_2\text{H}$.

The term "carbonyl", whether used alone or with other
25 terms, such as "aminocarbonyl", denotes -(C=O)- .

The term "aminocarbonyl" denotes an amide group of the
formula -C(=O)NH_2 .

The terms "N-alkylaminocarbonyl" and "N,N-
dialkylaminocarbonyl" denote aminocarbonyl radicals
30 independently substituted with one or two alkyl radicals,
respectively. More preferred are "lower alkylaminocarbonyl"
having lower alkyl radicals as described above attached to
an aminocarbonyl radical.

The terms "N-arylaminoacarbonyl" and "N-alkyl-N-arylaminoacarbonyl" denote aminocarbonyl radicals substituted, respectively, with one aryl radical, or one alkyl and one aryl radical.

5 The term "heterocyclylcarbonylalkyl" denotes alkyl groups which have been substituted with a heterocyclylcarbonyl radical. More preferred are contain 4-6 membered heterocyclyl groups and C₁-C₆-alkyl radicals, such as 4-methylpiperazinyllcarbonylethyl.

10 The term "heterocyclylalkylcarbonyl" denotes carbonyl groups which have been substituted with a heterocyclylalkyl radical. More preferred are contain 4-6 membered heterocyclyl groups and C₁-C₆-alkyl radicals, such as piperidinyllmethylcarbonyl.

15 The term "alkoxycarbonylaminoalkyl" denotes an aminoalkyl group, which is substituted with an alkoxycarbonyl radical. More preferred are "lower alkoxycarbonylaminoalkyl" having C₁-C₆-alkyl radicals.

20 The term "heterocyclylalkylenyl" embraces heterocyclic-substituted alkyl radicals. More preferred heterocyclylalkylenyl radicals are "5- or 6-membered heteroarylalkylenyl" radicals having alkyl portions of one to six carbon atoms and a 5- or 6-membered heteroaryl radical. Even more preferred are lower heteroarylalkylenyl radicals having alkyl portions of one to four carbon atoms. Examples include such radicals as pyridylmethyl and thienylmethyl.

30 The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Even more preferred are "phenylalkylenyl" attached to alkyl portions having one to three carbon atoms. Examples of such radicals include benzyl, diphenylmethyl and phenylethyl. The aryl in said

aralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more preferred are lower alkylthio radicals having one to three carbon atoms. An example of "alkylthio" is methylthio, (CH₃S-).

The term "haloalkylthio" embraces radicals containing a haloalkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more preferred are lower haloalkylthio radicals having one to three carbon atoms. An example of "haloalkylthio" is trifluoromethylthio.

The term "alkylamino" embraces "N-alkylamino" and "N,N-dialkylamino" where amino groups are independently substituted with one alkyl radical and with two alkyl radicals, respectively. More preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Even more preferred are lower alkylamino radicals having one to three carbon atoms. Suitable alkylamino radicals may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino and the like.

The term "arylamino" denotes amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. The arylamino radicals may be further substituted on the aryl ring portion of the radical.

The term "heteroarylamino" denotes amino groups which have been substituted with one or two heteroaryl radicals, such as N-thienylamino. The "heteroarylamino" radicals may be further substituted on the heteroaryl ring portion of the radical.

The term "aralkylamino" denotes amino groups which have been independently substituted with one or two aralkyl radicals. More preferred are phenyl-C₁-C₃-alkylamino radicals, such as N-benzylamino. The aralkylamino radicals
5 may be further substituted on the aryl ring portion.

The terms "N-alkyl-N-arylamino" and "N-aralkyl-N-alkylamino" denote amino groups which are independently substituted with one aralkyl and one alkyl radical, or one aryl and one alkyl radical, respectively, to an amino group.

10 The term "aminoalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more amino radicals. More preferred aminoalkyl radicals are "lower aminoalkyl" radicals having one to six carbon atoms and one or more
15 amino radicals. Examples of such radicals include aminomethyl, aminoethyl, aminopropyl, aminobutyl and aminohexyl. Even more preferred are lower aminoalkyl radicals having one to three carbon atoms.

The term "alkylaminoalkyl" embraces alkyl radicals
20 substituted with alkylamino radicals. More preferred alkylaminoalkyl radicals are "lower alkylaminoalkyl" radicals having alkyl radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkyl radicals having alkyl radicals of one to three carbon atoms. Suitable
25 alkylaminoalkyl radicals may be mono or dialkyl substituted, such as N-methylaminomethyl, N,N-dimethyl-aminoethyl, N,N-diethylaminomethyl and the like.

The term "alkylaminoalkoxy" embraces alkoxy radicals substituted with alkylamino radicals. More preferred
30 alkylaminoalkoxy radicals are "lower alkylaminoalkoxy" radicals having alkoxy radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkoxy radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkoxy radicals may be mono or dialkyl

substituted, such as N-methylaminoethoxy, N,N-dimethylaminoethoxy, N,N-diethylaminoethoxy and the like.

The term "alkylaminoalkoxyalkoxy" embraces alkoxy radicals substituted with alkylaminoalkoxy radicals. More preferred alkylaminoalkoxyalkoxy radicals are "lower alkylaminoalkoxyalkoxy" radicals having alkoxy radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkoxyalkoxy radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkoxyalkoxy radicals may be mono or dialkyl substituted, such as N-methylaminoethoxyethoxy, N-methylaminomethoxyethoxy, N,N-dimethylaminoethoxyethoxy, N,N-diethylaminomethoxymethoxy and the like.

The term "carboxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more carboxy radicals. More preferred carboxyalkyl radicals are "lower carboxyalkyl" radicals having one to six carbon atoms and one carboxy radical. Examples of such radicals include carboxymethyl, carboxypropyl, and the like. Even more preferred are lower carboxyalkyl radicals having one to three CH₂ groups.

The term "halosulfonyl" embraces sulfonyl radicals substituted with a halogen radical. Examples of such halosulfonyl radicals include chlorosulfonyl and fluorosulfonyl.

The term "arylthio" embraces aryl radicals of six to ten carbon atoms, attached to a divalent sulfur atom. An example of "arylthio" is phenylthio.

The term "aralkylthio" embraces aralkyl radicals as described above, attached to a divalent sulfur atom. More preferred are phenyl-C₁-C₃-alkylthio radicals. An example of "aralkylthio" is benzylthio.

The term "aryloxy" embraces optionally substituted aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy.

5 The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are "lower aralkoxy" radicals having optionally substituted phenyl radicals attached to lower alkoxy radical as described above.

10 The term "heteroaryloxy" embraces optionally substituted heteroaryl radicals, as defined above, attached to an oxygen atom.

The term "heteroarylalkoxy" embraces oxy-containing heteroarylalkyl radicals attached through an oxygen atom to other radicals. More preferred heteroarylalkoxy radicals are 15 "lower heteroarylalkoxy" radicals having optionally substituted heteroaryl radicals attached to lower alkoxy radical as described above.

The term "cycloalkyl" includes saturated carbocyclic groups. Preferred cycloalkyl groups include C₃-C₆ rings. 20 More preferred compounds include, cyclopentyl, cyclopropyl, and cyclohexyl.

The term "cycloalkylalkyl" embraces cycloalkyl-substituted alkyl radicals. Preferable cycloalkylalkyl radicals are "lower cycloalkylalkyl" radicals having C₃₋₆ 25 cycloalkyl radicals attached to alkyl radicals having one to six carbon atoms.

The term "cycloalkenyl" includes carbocyclic groups having one or more carbon-carbon double bonds including "cycloalkyldienyl" compounds. Preferred cycloalkenyl groups 30 include C₃-C₆ rings. More preferred compounds include, for example, cyclopentenyl, cyclopentadienyl, cyclohexenyl and cycloheptadienyl.

The term "comprising" is meant to be open ended, including the indicated component but not excluding other elements.

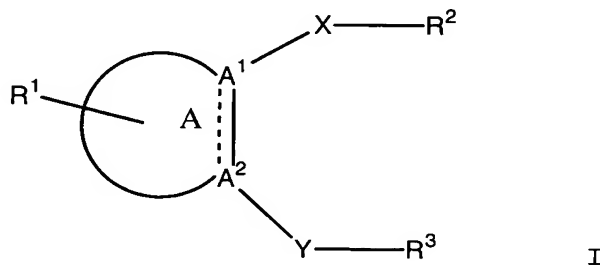
The term "Formulas I-IV" includes formula II'.

5 The compounds of the invention are endowed with kinase inhibitory activity, such as KDR inhibitory activity.

The present invention also comprises the use of a compound of the invention, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the
10 treatment either acutely or chronically of an angiogenesis mediated disease state, including those described previously. The compounds of the present invention are useful in the manufacture of an anti-cancer medicament. The compounds of the present invention are also useful in the
15 manufacture of a medicament to attenuate or prevent disorders through inhibition of KDR.

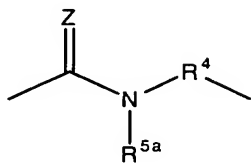
The present invention comprises a pharmaceutical composition comprising a therapeutically-effective amount of a compound of Formulas I-IV in association with a least one
20 pharmaceutically-acceptable carrier, adjuvant or diluent.

The present invention also comprises a method of treating angiogenesis related disorders in a subject having or susceptible to such disorder, the method comprising treating the subject with a therapeutically-effective amount
25 of a compound of Formula I



wherein each of A^1 and A^2 is independently C or N;

wherein A¹-A² form part of a ring A selected from 5- or 6-membered heteroaryl;

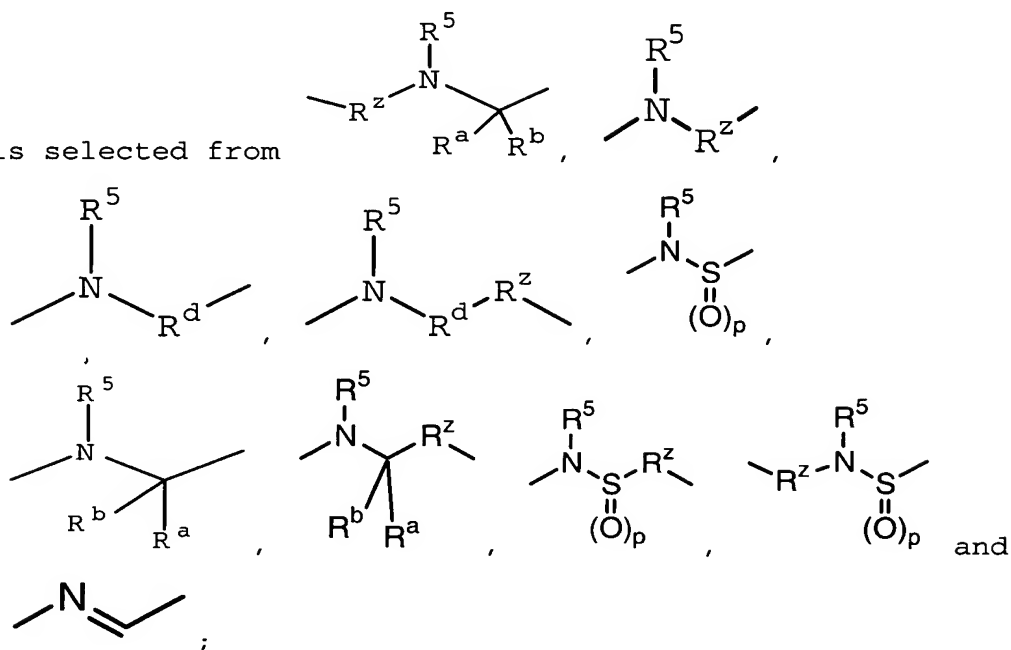


wherein X is

;

wherein Z is oxygen or sulfur;

5 Y is selected from



10 wherein p is 0 to 2,

wherein R^a and R^b are independently selected from H, halo, cyano, -NHR⁶ and C₁₋₄-alkyl substituted with R¹, or wherein R^a and R^b together form C₃-C₆ cycloalkyl;

15 wherein R^z is selected from C₂-C₆-alkylenyl, where one of the CH₂ groups may be replaced with an oxygen atom or an -NH-; wherein one of the CH₂ groups may be substituted with one or two radicals selected from halo, cyano, -NHR⁶ and C₁₋₄-alkyl substituted with R¹;

wherein R^d is cycloalkyl;

20 wherein R¹ is one or more substituents independently selected from H, halo, -OR⁷, oxo, -SR⁷, -CO₂R⁷, -COR⁷, -

CONR⁷R⁷, -NR⁷R⁷, -SO₂NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, -
NR⁷C(O)NR⁷R⁷, cycloalkyl, optionally substituted
phenylalkylenyl, optionally substituted 5-6 membered
heterocyclyl, optionally substituted heteroarylalkylenyl,
5 optionally substituted phenyl, lower alkyl, cyano, lower
hydroxyalkyl, lower carboxyalkyl, nitro, lower alkenyl,
lower alkynyl, lower aminoalkyl, lower alkylaminoalkyl
and lower haloalkyl;

wherein R² is selected from

- 10 a) substituted or unsubstituted 6-10 membered aryl,
b) substituted or unsubstituted 5-6 membered
heterocyclyl,
c) substituted or unsubstituted 9-14 membered bicyclic or
tricyclic heterocyclyl,
15 d) cycloalkyl, and
e) cycloalkenyl,

wherein substituted R² is substituted with one or more
substituents independently selected from halo, -OR⁷, -
SR⁷, -CO₂R⁷, -CONR⁷R⁷, -COR⁷, -NR⁷R⁷, -NH(C₁-C₄
20 alkylenylR⁹), -SO₂R⁷, -SO₂NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷,
optionally substituted cycloalkyl, optionally
substituted 5-6 membered heterocyclyl, optionally
substituted phenyl, halosulfonyl, cyano,
alkylaminoalkoxy, alkylaminoalkoxyalkoxy, nitro, lower
25 alkyl substituted with R¹, lower alkenyl substituted
with R¹, and lower alkynyl substituted with R¹;

wherein R³ is selected from aryl substituted with one or
more substituents independently selected from halo, -OR⁷,
-SR⁷, -SO₂R⁷, -CO₂R⁷, -CONR⁷R⁷, -COR⁷, -NR⁷R⁷, -SO₂NR⁷R⁷, -
30 NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, cycloalkyl, optionally substituted
5-6 membered heterocyclyl, optionally substituted phenyl,
nitro, alkylaminoalkoxyalkoxy, cyano, alkylaminoalkoxy,
lower alkyl substituted with R¹, lower alkenyl

substituted with R¹, and lower alkynyl substituted with R¹;

wherein R⁴ is selected from a direct bond, C₂₋₄-alkylenyl, C₂₋₄-alkenylenyl and C₂₋₄-alkynylenyl, where one of the CH₂

5 groups may be substituted with an oxygen atom or an -NH-, wherein R⁴ is optionally substituted with hydroxy;

wherein R⁵ is selected from H, lower alkyl, phenyl and lower aralkyl;

10 wherein R^{5a} is selected from H, lower alkyl, phenyl and lower aralkyl;

wherein R⁶ is selected from H or C₁₋₆-alkyl; and

wherein R⁷ is selected from H, lower alkyl, phenyl, 5-6 membered heterocyclyl, C₃-C₆-cycloalkyl, phenylalkyl, 5-6 membered heterocyclylalkyl, C₃-C₆ cycloalkylalkyl, and

15 lower haloalkyl;

wherein R⁹ is selected from H, phenyl, 5-6 membered heterocyclyl and C₃-C₆ cycloalkyl.

COMBINATIONS

20

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more compounds of the invention or other agents. When administered as a
25 combination, the therapeutic agents can be formulated as separate compositions that are administered at the same time or sequentially at different times, or the therapeutic agents can be given as a single composition.

The phrase "co-therapy" (or "combination-therapy"), in
30 defining use of a compound of the present invention and another pharmaceutical agent, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-
35 administration of these agents in a substantially

simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent.

Specifically, the administration of compounds of the present invention may be in conjunction with additional therapies known to those skilled in the art in the prevention or treatment of neoplasia, such as with radiation therapy or with cytostatic or cytotoxic agents.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the accepted dosage ranges. Compounds of Formulas I-IV may also be administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of the invention may be administered either prior to, simultaneous with, or after administration of the known anticancer or cytotoxic agent.

Currently, standard treatment of primary tumors consists of surgical excision followed by either radiation or IV administered chemotherapy. The typical chemotherapy regime consists of either DNA alkylating agents, DNA intercalating agents, CDK inhibitors, or microtubule poisons. The chemotherapy doses used are just below the maximal tolerated dose and therefore dose limiting toxicities typically include, nausea, vomiting, diarrhea, hair loss, neutropenia and the like.

There are large numbers of antineoplastic agents available in commercial use, in clinical evaluation and in pre-clinical development, which would be selected for treatment of neoplasia by combination drug chemotherapy. Such antineoplastic agents fall into several major categories, namely, antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents,

immunological agents, interferon-type agents and a category of miscellaneous agents.

A first family of antineoplastic agents which may be used in combination with compounds of the present invention consists of antimetabolite-type/thymidilate synthase inhibitor antineoplastic agents. Suitable antimetabolite antineoplastic agents may be selected from but not limited to the group consisting of 5-FU-fibrinogen, acanthifolic acid, aminothiadiazole, brequinar sodium, carmofur, Ciba-Geigy CGP-30694, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, Lilly DATHF, Merrel Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, doxifluridine, Wellcome EHNA, Merck & Co. EX-015, fazarabine, floxuridine, fludarabine phosphate, 5-fluorouracil, N-(2'-furanidyl)-5-fluorouracil, Daiichi Seiyaku FO-152, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim, methotrexate, Wellcome MZPES, norspermidine, NCI NSC-127716, NCI NSC-264880, NCI NSC-39661, NCI NSC-612567, Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi Chemical PL-AC, Takeda TAC-788, thioguanine, tiazofurin, Erbamont TIF, trimetrexate, tyrosine kinase inhibitors, Taiho UFT and uricytin.

A second family of antineoplastic agents which may be used in combination with compounds of the present invention consists of alkylating-type antineoplastic agents. Suitable alkylating-type antineoplastic agents may be selected from but not limited to the group consisting of Shionogi 254-S, aldo-phosphamide analogues, altretamine, anaxirone, Boehringer Mannheim BBR-2207, bestrabucil, budotitane, Wakunaga CA-102, carboplatin, carmustine, Chinoin-139, Chinoin-153, chlorambucil, cisplatin, cyclophosphamide, American Cyanamid CL-286558, Sanofi CY-233, cyplatate, Degussa D-19-384, Sumimoto DACHP(My^r)₂, diphenylspiromustine, diplatinum cytostatic, Erba distamycin

derivatives, Chugai DWA-2114R, ITI E09, elmustine, Erbamont FCE-24517, estramustine phosphate sodium, fotemustine, Unimed G-6-M, Chinoin GYKI-17230, hepsul-fam, ifosfamide, iproplatin, lomustine, mafosfamide, mitolactol, Nippon
5 Kayaku NK-121, NCI NSC-264395, NCI NSC-342215, oxaliplatin, Upjohn PCNU, prednimustine, Proter PTT-119, ranimustine, semustine, SmithKline SK&F-101772, Yakult Honsha SN-22, spiromus-tine, Tanabe Seiyaku TA-077, tauromustine, temozolomide, teroxirone, tetraplatin and trimelamol.

10 A third family of antineoplastic agents which may be used in combination with compounds of the present invention consists of antibiotic-type antineoplastic agents. Suitable antibiotic-type antineoplastic agents may be selected from but not limited to the group consisting of Taiho 4181-A,
15 aclarubicin, actinomycin D, actinoplanone, Erbamont ADR-456, aeroplysinin derivative, Ajinomoto AN-201-II, Ajinomoto AN-3, Nippon Soda anisomycins, anthracycline, azino-mycin-A, bisucaberin, Bristol-Myers BL-6859, Bristol-Myers BMY-25067, Bristol-Myers BMY-25551, Bristol-Myers BMY-26605, Bristol-
20 Myers BMY-27557, Bristol-Myers BMY-28438, bleomycin sulfate, bryostatin-1, Taiho C-1027, caliche mycin, chromoximycin, dactinomycin, daunorubicin, Kyowa Hakko DC-102, Kyowa Hakko DC-79, Kyowa Hakko DC-88A, Kyowa Hakko DC89-A1, Kyowa Hakko DC92-B, ditrisarubicin B, Shionogi DOB-41, doxorubicin,
25 doxorubicin-fibrinogen, elsamicin-A, epirubicin, erbstatin, esorubicin, esperamicin-A1, esperamicin-Alb, Erbamont FCE-21954, Fujisawa FK-973, fostriecin, Fujisawa FR-900482, glidobactin, gregatin-A, grincamycin, herbimycin, idarubicin, illudins, kazusamycin, kesarirhodins, Kyowa
30 Hakko KM-5539, Kirin Brewery KRN-8602, Kyowa Hakko KT-5432, Kyowa Hakko KT-5594, Kyowa Hakko KT-6149, American Cyanamid LL-D49194, Meiji Seika ME 2303, menogaril, mitomycin, mitoxantrone, SmithKline M-TAG, neoenactin, Nippon Kayaku NK-313, Nippon Kayaku NKT-01, SRI International NSC-357704,

oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, porothramycin, pyrindanycin A, Tobishi RA-I, rapamycin, rhizoxin, rodorubicin, sibanomicin, siwenmycin, Sumitomo SM-5887, Snow Brand SN-706, Snow Brand SN-07, sorangicin-A, 5 sparsomycin, SS Pharmaceutical SS-21020, SS Pharmaceutical SS-7313B, SS Pharmaceutical SS-9816B, steffimycin B, Taiho 4181-2, talisomycin, Takeda TAN-868A, terpentecin, thrazine, tricrozarin A, Upjohn U-73975, Kyowa Hakko UCN-10028A, Fujisawa WF-3405, Yoshitomi Y-25024 and zorubicin.

10 A fourth family of antineoplastic agents which may be used in combination with compounds of the present invention consists of a miscellaneous family of antineoplastic agents, including tubulin interacting agents, topoisomerase II inhibitors, topoisomerase I inhibitors and hormonal agents, 15 selected from but not limited to the group consisting of α -carotene, α -difluoromethyl-arginine, acitretin, Biotec AD-5, Kyorin AHC-52, alstonine, amonafide, amphetinile, amsacrine, Angiostat, ankinomycin, anti-neoplaston A10, antineoplaston A2, antineoplaston A3, antineoplaston A5, 20 antineoplaston AS2-1, Henkel APD, aphidicolin glycinate, asparaginase, Avarol, baccharin, batracylin, benfluron, benzotript, Ipsen-Beaufour BIM-23015, bisantrene, Bristol-Myers BMY-40481, Vestar boron-10, bromofosfamide, Wellcome BW-502, Wellcome BW-773, caracemide, carmethizole 25 hydrochloride, Ajinomoto CDAF, chlorsulfaquinoxalone, Chemes CHX-2053, Chemex CHX-100, Warner-Lambert CI-921, Warner-Lambert CI-937, Warner-Lambert CI-941, Warner-Lambert CI-958, clanfenur, claviridenone, ICN compound 1259, ICN compound 4711, Contracan, Yakult Honsha CPT-11, crisnatol, 30 curaderm, cytochalasin B, cytarabine, cytocytin, Merz D-609, DABIS maleate, dacarbazine, datelliptinium, didemnin-B, dihaematoporphyrin ether, dihydrolenperone, dinaline, distamycin, Toyo Pharmar DM-341, Toyo Pharmar DM-75, Daiichi Seiyaku DN-9693, docetaxel elliprabatin, elliptinium acetate,

Tsumura EPMTTC, the epothilones, ergotamine, etoposide, etretinate, fenretinide, Fujisawa FR-57704, gallium nitrate, genkwadaphnin, Chugai GLA-43, Glaxo GR-63178, grifolan NMF-5N, hexadecylphosphocholine, Green Cross HO-221,

5 homoharringtonine, hydroxyurea, BTG ICRF-187, ilmofosine, isoglutamine, isotretinoin, Otsuka JI-36, Ramot K-477, Otsuak K-76COONa, Kureha Chemical K-AM, MECT Corp KI-8110, American Cyanamid L-623, leukoregulin, lonidamine, Lundbeck LU-23-112, Lilly LY-186641, NCI (US) MAP, marycin, Merrel

10 Dow MDL-27048, Medco MEDR-340, merbarone, merocyanine derivatives, methylanilinoacridine, Molecular Genetics MGI-136, minactivin, mitonafide, mitoguanine mepidamol, motretinide, Zenyaku Kogyo MST-16, N-(retinoyl)amino acids, Nisshin Flour Milling N-021, N-acylated-dehydroalanines,

15 nafazatrom, Taisho NCU-190, nocodazole derivative, Normosang, NCI NSC-145813, NCI NSC-361456, NCI NSC-604782, NCI NSC-95580, ocreotide, Ono ONO-112, oquizanocine, Akzo Org-10172, paclitaxel, pancratistatin, pazelliptine, Warner-Lambert PD-111707, Warner-Lambert PD-115934, Warner-Lambert

20 PD-131141, Pierre Fabre PE-1001, ICRT peptide D, piroxantrone, polyhaematoporphyrin, polypreic acid, Efamol porphyrin, probimane, procarbazine, proglumide, Invitron protease nexin I, Tobishi RA-700, razoxane, Sapporo Breweries RBS, restrictin-P, retelliptine, retinoic acid,

25 Rhone-Poulenc RP-49532, Rhone-Poulenc RP-56976, SmithKline SK&F-104864, Sumitomo SM-108, Kuraray SMANCS, SeaPharm SP-10094, spatol, spirocyclopropane derivatives, spirogermanium, Unimed, SS Pharmaceutical SS-554, strypoldinone, Stypoldione, Suntory SUN 0237, Suntory SUN

30 2071, superoxide dismutase, Toyama T-506, Toyama T-680, taxol, Teijin TEI-0303, teniposide, thaliblastine, Eastman Kodak TJB-29, tocotrienol, topotecan, Topostin, Teijin TT-82, Kyowa Hakko UCN-01, Kyowa Hakko UCN-1028, ukrain, Eastman Kodak USB-006, vinblastine sulfate, vincristine,

vindesine, vinestramide, vinorelbine, vintriptol, vinzolidine, withanolides and Yamanouchi YM-534.

Alternatively, the present compounds may also be used in co-therapies with other anti-neoplastic agents, such as

5 acemannan, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, amifostine, aminolevulinic acid, amrubicin, amsacrine, anagrelide, anastrozole, ANCER, ancestim, ARGLABIN, arsenic trioxide, BAM 002 (Novelos), bexarotene, bicalutamide, broxuridine, capecitabine,

10 celmoleukin, cetorelix, cladribine, clotrimazole, cytarabine ocfosfate, DA 3030 (Dong-A), daclizumab, denileukin diftitox, deslorelin, dexrazoxane, dilazep, docetaxel, docosanol, doxercalciferol, doxifluridine, doxorubicin, bromocriptine, carmustine, cytarabine,

15 fluorouracil, HIT diclofenac, interferon alfa, daunorubicin, doxorubicin, tretinoin, edelfosine, edrecolomab, eflornithine, emitefur, epirubicin, epoetin beta, etoposide phosphate, exemestane, exisulind, fadrozole, filgrastim, finasteride, fludarabine phosphate,

20 formestane, fotemustine, gallium nitrate, gemcitabine, gemtuzumab zogamicin, gimeracil/oteracil/tegafur combination, glycopine, goserelin, heptaplatin, human chorionic gonadotropin, human fetal alpha fetoprotein, ibandronic acid, idarubicin, (imiquimod, interferon alfa,

25 interferon alfa, natural, interferon alfa-2, interferon alfa-2a, interferon alfa-2b, interferon alfa-N1, interferon alfa-n3, interferon alfacon-1, interferon alpha, natural, interferon beta, interferon beta-1a, interferon beta-1b, interferon gamma, natural interferon gamma-1a, interferon

30 gamma-1b, interleukin-1 beta, iobenguane, irinotecan, irsogladine, lanreotide, LC 9018 (Yakult), leflunomide, lenograstim, lentinan sulfate, letrozole, leukocyte alpha interferon, leuprorelin, levamisole + fluorouracil, liarozole, lobaplatin, lonidamine, lovastatin, masoprocol,

melarsoprol, metoclopramide, mifepristone, miltefosine, mirimostim, mismatched double stranded RNA, mitoguazone, mitolactol, mitoxantrone, molgramostim, nafarelin, naloxone + pentazocine, nartograstim, nedaplatin, nilutamide, 5 noscapine, novel erythropoiesis stimulating protein, NSC 631570 octreotide, oprelvekin, osaterone, oxaliplatin, paclitaxel, pamidronic acid, pegaspargase, peginterferon alfa-2b, pentosan polysulfate sodium, pentostatin, picibanil, pirarubicin, rabbit antithymocyte polyclonal 10 antibody, polyethylene glycol interferon alfa-2a, porfimer sodium, raloxifene, raltitrexed, rasburicase, rhenium Re 186 etidronate, RII retinamide, rituximab, romurtide, samarium (153 Sm) lexidronam, sargramostim, sizofiran, sobuzoxane, sonermin, strontium-89 chloride, suramin, 15 tasonermin, tazarotene, tegafur, temoporfin, temozolomide, teniposide, tetrachlorodecaoxide, thalidomide, thymalfasin, thyrotropin alfa, topotecan, toremifene, tositumomab-iodine 131, trastuzumab, treosulfan, tretinoin, trilostane, trimetrexate, triptorelin, tumor necrosis factor alpha, 20 natural, ubenimex, bladder cancer vaccine, Maruyama vaccine, melanoma lysate vaccine, valrubicin, verteporfin, vinorelbine, VIRULIZIN, zinostatin stimalamer, or zoledronic acid; abarelix; AE 941 (Aeterna), ambamustine, antisense oligonucleotide, bcl-2 (Genta), APC 8015 25 (Dendreon), cetuximab, decitabine, dexaminoglutethimide, diaziquone, EL 532 (Elan), EM 800 (Endorecherche), eniluracil, etanidazole, fenretinide, filgrastim SD01 (Amgen), fulvestrant, galocitabine, gastrin 17 immunogen, HLA-B7 gene therapy (Vical), granulocyte macrophage colony 30 stimulating factor, histamine dihydrochloride, ibritumomab tiuxetan, ilomastat, IM 862 (Cytran), interleukin-2, iproxifene, LDI 200 (Milkhaus), leridistim, lintuzumab, CA 125 MAb (Biomira), cancer MAb (Japan Pharmaceutical Development), HER-2 and Fc MAb (Medarex), idiotypic 105AD7

MAB (CRC Technology), idiotypic CEA MAB (Trilex), LYM-1-iodine 131 MAB (Techniclone), polymorphic epithelial mucin-
yttrium 90 MAB (Antisoma), marimastat, menogaril,
mitumomab, motexafin gadolinium, MX 6 (Galderma),
5 nelarabine, nolatrexed, P 30 protein, pegvisomant,
pemetrexed, porfiromycin, prinomastat, RL 0903 (Shire),
rubitecan, satraplatin, sodium phenylacetate, sparfosic
acid, SRL 172 (SR Pharma), SU 5416 (SUGEN), TA 077
(Tanabe), tetrathiomolybdate, thaliblastine,
10 thrombopoietin, tin ethyl etiopurpurin, tirapazamine,
cancer vaccine (Biomira), melanoma vaccine (New York
University), melanoma vaccine (Sloan Kettering Institute),
melanoma oncolysate vaccine (New York Medical College),
viral melanoma cell lysates vaccine (Royal Newcastle
15 Hospital), or valspodar.

Alternatively, the present compounds may also be used
in co-therapies with other anti-neoplastic agents, such as
other kinase inhibitors including p38 inhibitors and CDK
inhibitors, TNF inhibitors, metallomatrix proteases
20 inhibitors (MMP), COX-2 inhibitors including celecoxib,
rofecoxib, parecoxib, valdecoxib, and etoricoxib, NSAID's,
SOD mimics or $\alpha_v\beta_3$ inhibitors.

The present invention comprises processes for the
preparation of a compound of Formulas I-IV.

25 Also included in the family of compounds of Formulas
I-IV are the pharmaceutically-acceptable salts thereof. The
term "pharmaceutically-acceptable salts" embraces salts
commonly used to form alkali metal salts and to form
addition salts of free acids or free bases. The nature of
30 the salt is not critical, provided that it is
pharmaceutically-acceptable. Suitable pharmaceutically-
acceptable acid addition salts of compounds of Formulas I-IV
may be prepared from an inorganic acid or from an organic
acid. Examples of such inorganic acids are hydrochloric,

hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, arylaliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, adipic, butyric, 5 propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), 10 methanesulfonic, ethanesulfonic, ethanedisulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, camphoric, camphorsulfonic, digluconic, cyclopentanepropionic, dodecylsulfonic, glucoheptanoic, 15 glycerophosphonic, heptanoic, hexanoic, 2-hydroxyethanesulfonic, nicotinic, 2-naphthalenesulfonic, oxalic, palmoic, pectinic, persulfuric, 2-phenylpropionic, picric, pivalic propionic, succinic, tartaric, thiocyanic, mesylic, undecanoic, stearic, algenic, β -hydroxybutyric, salicylic, 20 galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formulas I-IV include metallic salts, such as salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc, or salts made from organic bases including primary, secondary 25 and tertiary amines, substituted amines including cyclic amines, such as caffeine, arginine, diethylamine, N-ethyl piperidine, histidine, glucamine, isopropylamine, lysine, morpholine, N-ethyl morpholine, piperazine, piperidine, triethylamine, trimethylamine. All of these salts may be 30 prepared by conventional means from the corresponding compound of the invention by reacting, for example, the appropriate acid or base with the compound of Formulas I-IV.

Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

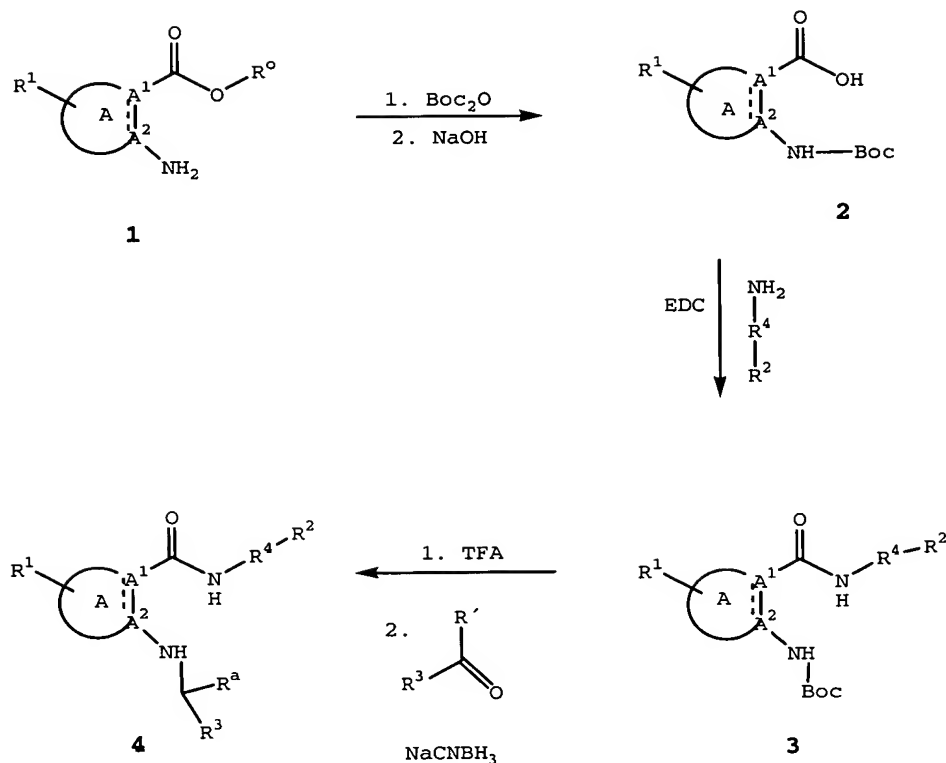
Examples of acids that may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Other examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases. Preferred salts include hydrochloride, phosphate and edisylate.

Additional examples of such salts can be found in Berge et al., J. Pharm. Sci., 66:1 (1977).

GENERAL SYNTHETIC PROCEDURES

The compounds of the invention can be synthesized according to the following procedures of Schemes 1-43, wherein the substituents are as defined for Formulas I-IV, above, except where further noted.

Scheme 1

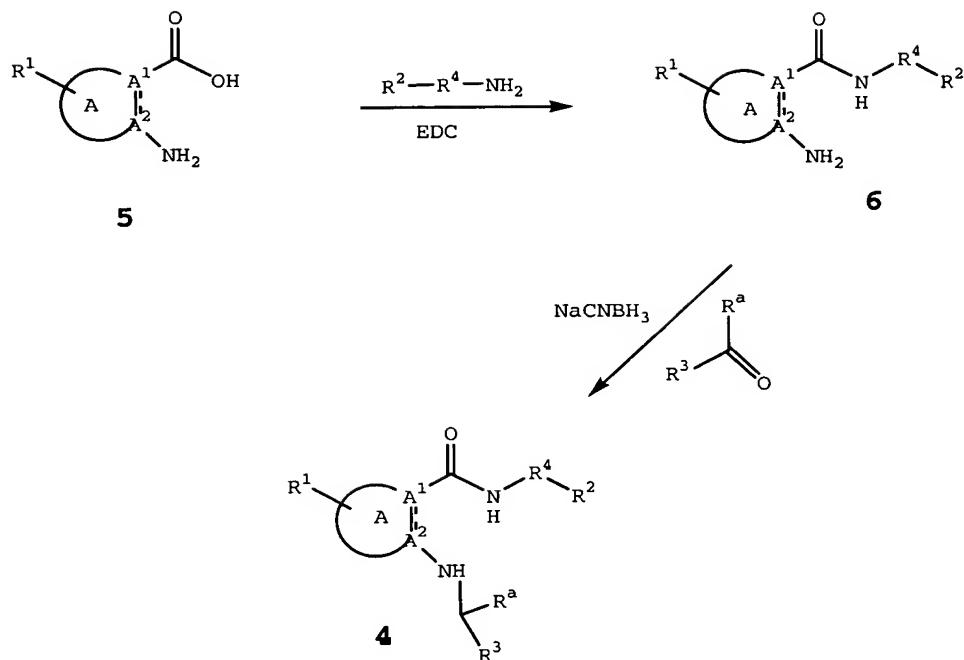


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Cyclic amides can be prepared according to the method set out in Scheme 1. The amino group of compound 1 (where R^o is alkyl, aryl, and the like) is protected, such as with Boc anhydride, followed by treatment, to remove the ester, such as with base, forming the protected amine/free acid 2. Alternatively, other amino protecting groups known in the art can be used. Substituted amines are coupled with the free acid, such as with EDC, to form the protected amine/amide 3. The protected amine moiety is removed, such as with acid, and reacted via one step reductive alkylation with carbonyl-containing compounds to form the 1-amido-2-substituted amino-compounds 4. Preferably the amination is in an alcohol, such as MeOH, EtOH or propanol, and at a temperature between about 0-50°C, such as RT. Aldehydes or ketones are preferred carbonyl-containing compounds.

Alternative carbonyl-containing compounds are, for example, bisulfite adducts or semiacetals, acetals, semiketals or ketals of compounds with alcohols, for example lower hydroxyalkyl compounds; or thioacetals or thioketals of compounds with mercaptans, for example lower alkylthio compounds. The reductive alkylation is preferably carried out with hydrogenation in the presence of a catalyst, such as platinum or especially palladium, which is preferably bonded to a carrier material, such as carbon, or a heavy metal catalyst, such as Raney nickel, at normal pressure or at pressures of from 0.1 to 10 MegaPascal (MPa), or with reduction by means of complex hydrides, such as borohydrides, especially alkali metal cyanoborohydrides, for example sodium cyanoborohydride, in the presence of a suitable acid, preferably relatively weak acids, such as lower alkylcarboxylic acids, especially acetic acid, or a sulfonic acid, such as p-toluenesulfonic acid; in customary solvents, for example alcohols, such as methanol or ethanol, or ethers, for example cyclic ethers, such as tetrahydrofuran, in the presence or absence of water.

Scheme 2



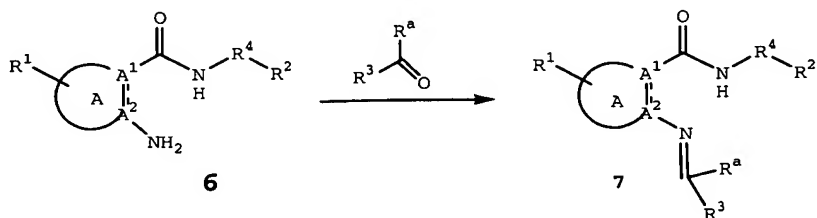
5

Alternatively, compounds **4** can be prepared from mixed acid/amines **5** as shown in Scheme 2. Substituted amines are coupled with the mixed acid/amines **5** such as with a coupling reagent, for example EDC, to form the mixed amine/amide **6**.

10 Substituted carbonyl compounds, such as acid halides, anhydrides, carboxylic acids, esters, ketones, aldehydes and the like, are added to the mixed amine/amide **6** followed with reduction to give the substituted amide/substituted amine compounds **4**.

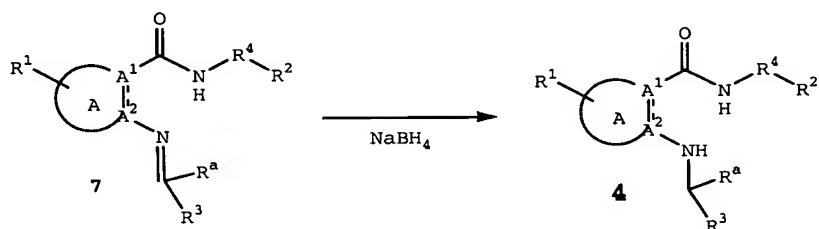
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Scheme 3



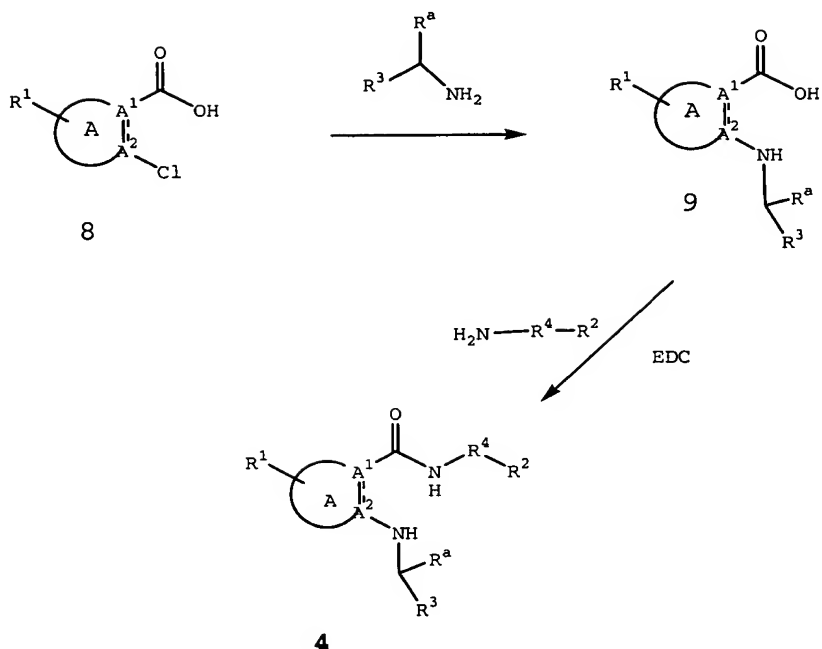
Imino compounds **7** can be formed from the mixed amine/amides **6**, such as by reacting with a substituted carbonyl compound.

5

Scheme 4

10 Substituted cyclic carboxamides can be prepared from the corresponding imino analogs by the process outlined in Scheme 4. Treatment of the imino compound **7** with a reducing agent yields compound **4**. Reagents which can be used to add hydrogen to an imine double bond include borane in THF,
15 LiAlH₄, NaBH₄, sodium in EtOH and hydrogen in the presence of a catalyst, among others.

Scheme 5



5 Substituted carboxamides **4** can be prepared from the
corresponding halo analogs **8** by the process outlined in
Scheme 5. Substituted amino acids **9** are prepared from the
corresponding chloro compounds **8** such as by reacting with an
amine at a suitable temperature, such as about 80°C. The
10 acid **9** is coupled with an amine, preferably in the presence
of a coupling agent such as EDC, to form the corresponding
amide **4**.

15 The amination process can be carried out as an Ullmann
type reaction using a copper catalyst, such as copper[0] or
a copper[I] compound such as copper[I]oxide,
copper[I]bromide or copper[I]iodide in the presence of a
suitable base (such as a metal carbonate, for example K₂CO₃)
to neutralize the acid generated in the reaction. This
reaction is reviewed in Houben-Weyl "Methoden der
20 Organischen Chemie", Band 11/1, page 32-33, 1958, in

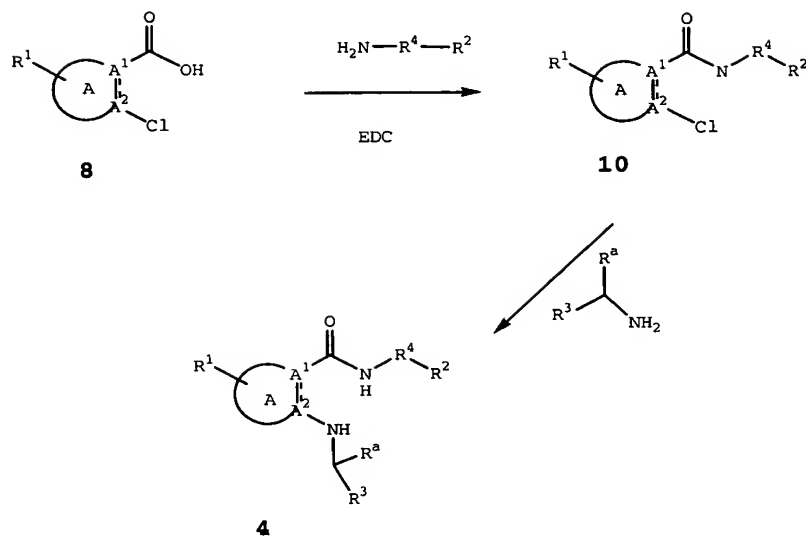
Organic Reactions, 14:19-24 (1965) and by J. Lindley in Tetrahedron, 40:1433-1456 (1984). The amount of catalyst is typically in the range of 1 to 20 mole percent. The reaction is carried out in an inert, aprotic solvent such as
5 an ether (for example, dimethoxyethane or dioxane) or an amide (for example dimethylformamide or *N*-methylpyrrolidone), under an inert atmosphere in the temperature range of 60-180 °C.

An alternative amination process involves using a
10 Group VIII element, where the metal core of the catalyst should be a zero-valent transition metal, such as palladium or nickel, which has the ability to undergo oxidative addition to the aryl-halogen bond. The zero valent state of the metal may be generated *in situ* from the M[II] state. The
15 catalyst complexes may include chelating ligands, such as alkyl, aryl or heteroaryl derivatives of phosphines or biphosphines, imines or arsines. Preferred catalysts contain palladium or nickel. Examples of such catalysts include palladium[II]chloride, palladium[II]acetate,
20 tetrakis(triphenyl-phosphine)palladium[0] and nickel[II]acetylacetonate. The metal catalyst is typically in the range of 0.1 to 10 mole percent. The chelating ligands may be either monodentate, as in the case for example of trialkylphosphines, such as tributylphosphine,
25 triarylphosphines, such as tri-(*ortho*-tolyl)phosphine, and triheteroaryl phosphines, such as tri-2-furylphosphine; or they may be bidentate such as in the case of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, 1,2-bis(diphenylphosphino)ethane, 1,1'-
30 bis(diphenylphosphino)ferrocene and 1-(*N,N*-dimethyl-amino)-1'-(dicyclohexylphosphino)biphenyl. The supporting ligand may be complexed to the metal center in the form of a metal complex prior to being added to the reaction mixture or may be added to the reaction mixture as a separate compound. The

supporting ligand is typically present in the range 0.01 to 20 mole percent. It is often necessary to add a suitable base to the reaction mixture, such as a trialkylamine (for example DIEA or 1,5-diazabicyclo[5,4,0]undec-5-ene), a Group I alkali metal alkoxide (for example potassium *tert*-butoxide) or carbonate (for example cesium carbonate) or potassium phosphate. The reaction is typically carried out in an inert aprotic solvent such as an ether (for example, dimethoxyethane or dioxane) or an amide (for example DMF or *N*-methylpyrrolidone), under an inert atmosphere in the temperature range of 60-180 °C.

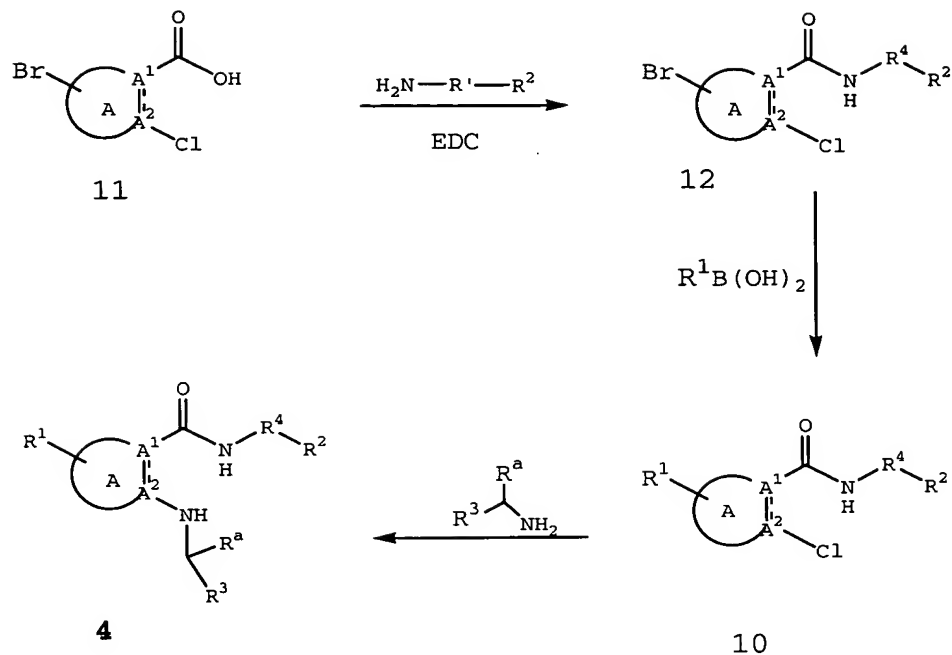
The amination is preferably carried out in an inert, aprotic, preferably anhydrous, solvent or solvent mixture, for example in a carboxylic acid amide, for example dimethylformamide or dimethylacetamide, a cyclic ether, for example THF or dioxane, or a nitrile, for example CH₃CN, or in a mixture thereof, at an appropriate temperature, for example in a temperature range of from about 40 °C to about 180 °C, and if necessary under an inert gas atmosphere, for example a nitrogen or argon atmosphere.

Scheme 6



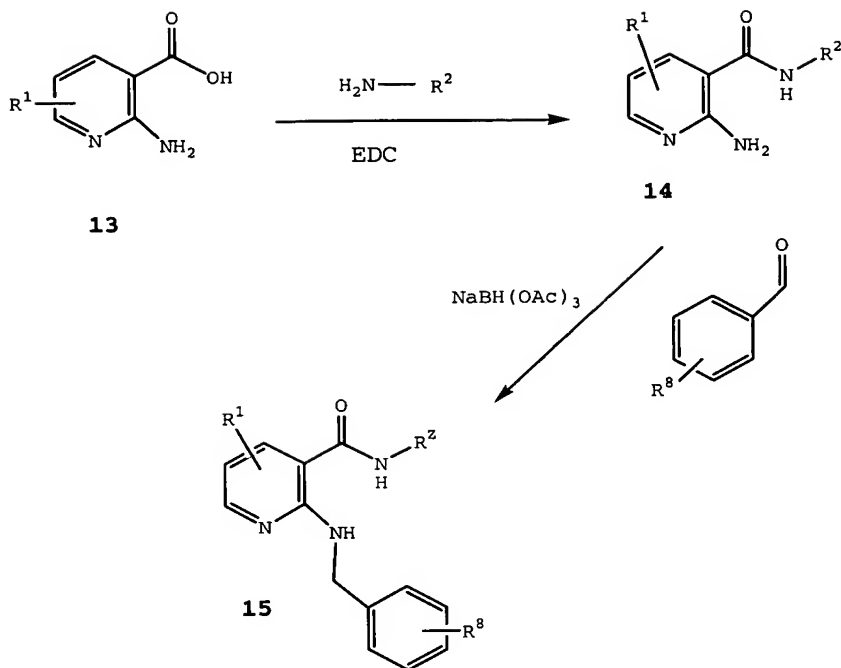
- 5 Substituted carboxamides **4** can be prepared from the corresponding halo analogs **8** by the process outlined in Scheme 6. The chloro acid **8** is coupled with an amine, preferably in the presence of a coupling agent such as EDC, to form the corresponding chloro amide **10**. Substituted
- 10 amino-amides **4** are prepared from the corresponding chloro compounds **10** such as by reacting with an amine at a suitable temperature, such as about 80 °C. The amination reaction can be run in the presence of an appropriate catalyst such as a palladium catalyst, in the presence of an aprotic base such
- 15 as sodium *t*-butoxide or cesium carbonate, or a nickel catalyst, or a copper catalyst.

Scheme 7



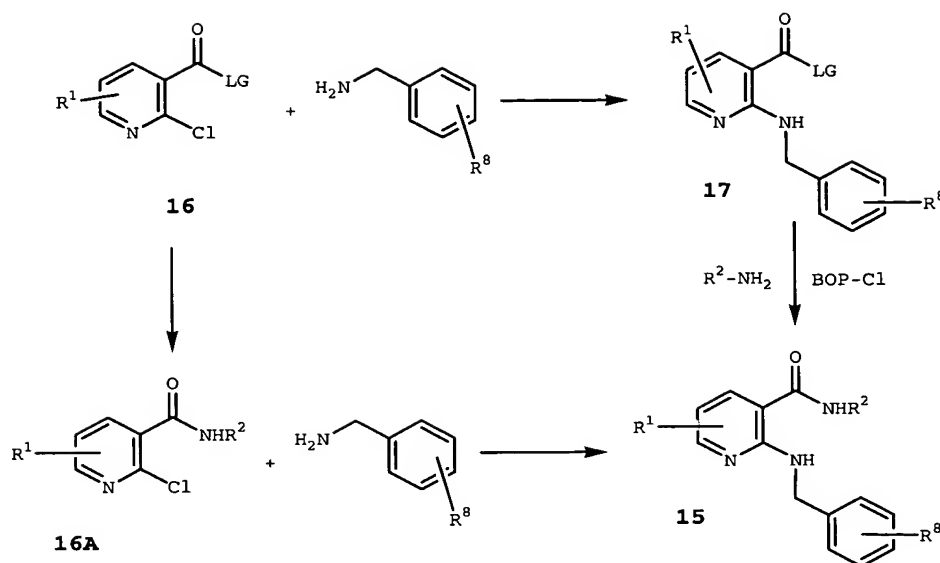
5 Substituted carboxamides **4** can be prepared from the corresponding bromo/chloro analogs **11** by the process outlined in Scheme 7. The bromo/chloro acid **11** is coupled with an amine, preferably in the presence of a coupling agent such as EDC, to form the corresponding bromo
10 substituted amide **12**. Suzuki coupling with the bromo amide **12** and suitable boronic acids provides the substituted amide **10**. Substituted amino-amides **4** are prepared from the corresponding chloro compounds **10** as described in Scheme 6.

Scheme 8



- 5 Substituted pyridines can be prepared such as by the method found in Scheme 8. 2-Aminonicotinic acid **13** is coupled with a substituted amine at a suitable temperature, nonprotic solvent such as CH_2Cl_2 , such as with EDC and HOBT, to form the nicotinamide **14**. The nicotinamide **14** is
- 10 reductively alkylated such as with substituted 4-benzaldehydes and $\text{NaBH}(\text{OAc})_3$, to yield the 2-substituted amino-pyridyl carboxamides **15**.

Scheme 9

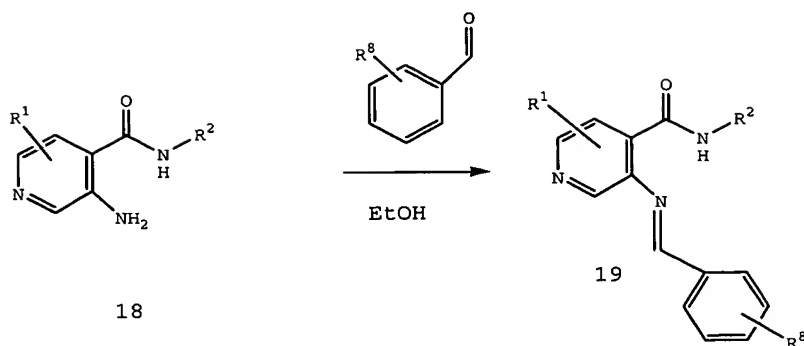


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Substituted pyridines may be prepared by the method found in Scheme 9. 2-Chloro-nicotinic acid **16** (where LG is OH) is coupled with an amine at a suitable temperature, such as a temperature over about 100 °C to give the 2-substituted amino-nicotinic acid **17**. The 2-substituted amino-nicotinic acid **17** is reacted with a substituted amine in the presence of a coupling reagent, such as BOP-Cl and base, such as TEA to form the 2-substituted amino-nicotinamide **15**.

Alternatively, 2-chloro-nicotinoyl chloride (LG is Cl) is coupled first with R²-NH₂, such as in the presence of base, e.g., NaHCO₃, in a suitable solvent, such as CH₂Cl₂, to form the amide **16A**, then coupled with a benzylamine to yield the 2-substituted amino-nicotinamide **15**.

Scheme 10

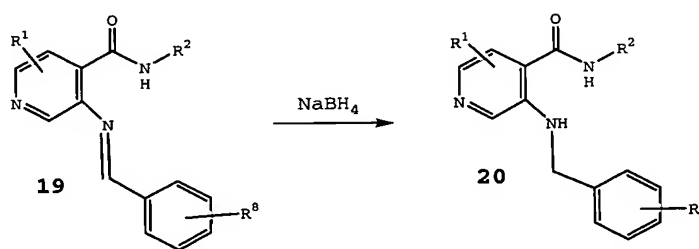


5

Imino-substituted pyridines may be prepared by the method found in Scheme 10. (2-Amino-(4-pyridyl))-carboxamide **18** is reacted with substituted 4-benzaldehydes, such as in the presence of p-toluenesulfonic acid monohydrate to yield the imino compound **19**.

10

Scheme 11

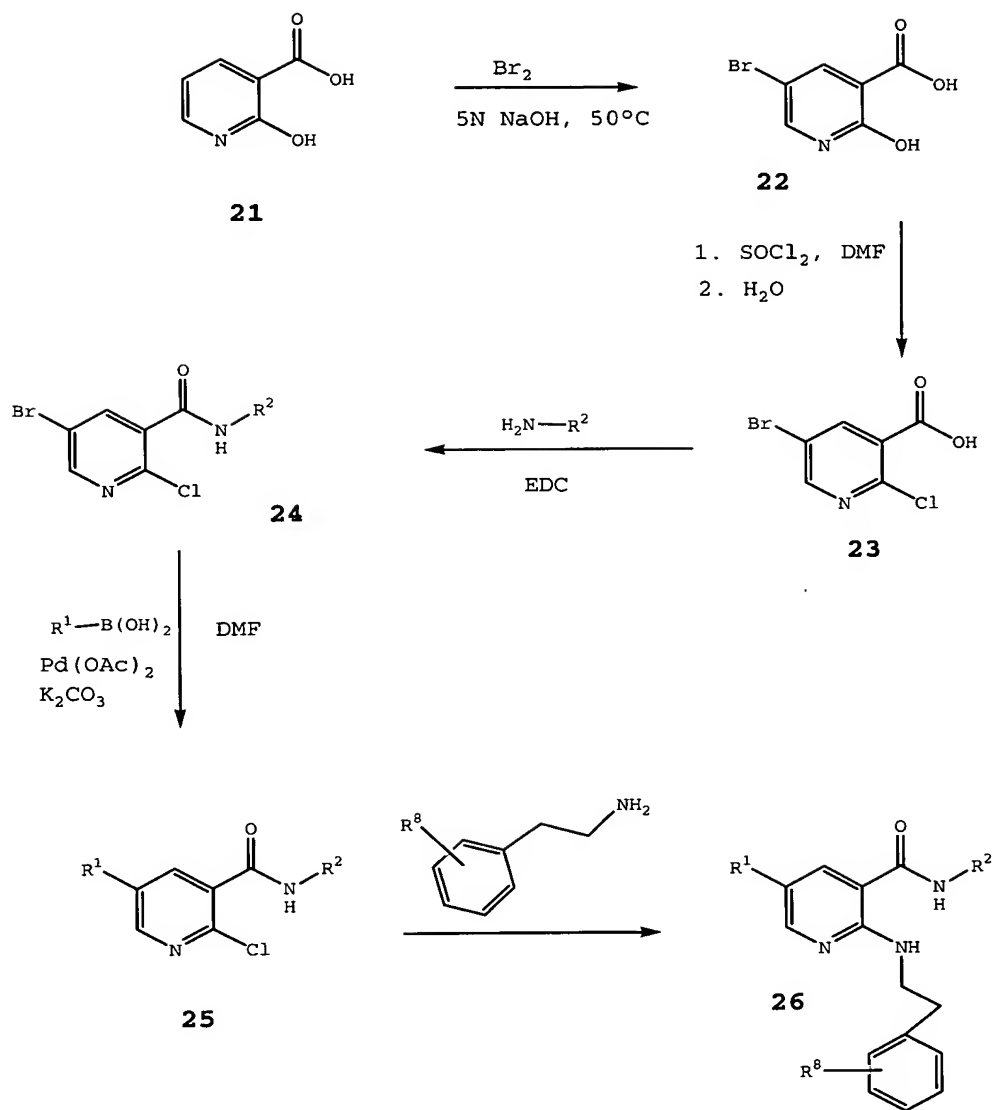


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Substituted pyridines alternatively may be prepared by the method found in Scheme 11. The imino compound **19** is reduced, such as with NaBH₄, to form the substituted amine **20**.

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Scheme 12



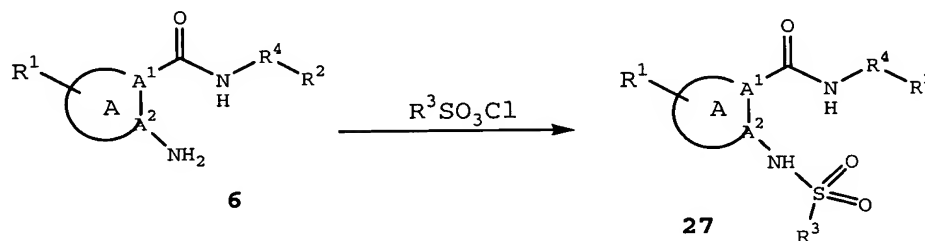
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Substituted pyridines can be prepared by the process outlined in Scheme 12. A solution of sodium hypobromite is freshly prepared and added to 2-hydroxynicotinic acid **21** and heated, preferably at a temperature at about 50 °C.

10 Additional hypobromite solution may be needed to form the bromo compound **22**. The 5-bromo-2-hydroxynicotinic acid **22**

is reacted with thionyl chloride, preferably at a temperature $> RT$, more preferably at about $80\text{ }^{\circ}C$ to form the 2-chloro-nicotinic acid analog **23**. The acid is coupled with an amine, preferably in the presence of EDC, HOBT, and DIEA to form the corresponding substituted amide **24**. Suzuki coupling with the bromo amide and suitable boronic acids, provides the substituted nicotinamide **25**. 2-Amino-nicotinamides **26** are prepared from the corresponding chloro compounds **25** such as by reacting with substituted amines at a suitable temperature, such as about $80\text{ }^{\circ}C$.

Scheme 13



15

Alternatively, sulfonamides **27** can be prepared from amines **6** as shown in Scheme 13. Substituted sulfonyl compounds, such as sulfonyl halides, preferably chloro or bromo, sulfonic acids, an activated ester or reactive anhydride, or in the form of a cyclic amide, and the like, are added to the amine **6** to give the sulfonamide compounds **27**.

The reaction is carried out in a suitable solvent, such as CH_2Cl_2 , at a temperature between about RT to about the reflux temperature of the solvent, in the presence of a suitable base, such as DIEA or DMAP.

The amino group of compounds **6** is preferably in free form, especially when the sulfonyl group reacting therewith is present in reactive form. The amino group may, however, itself be a derivative, for example by reaction with a

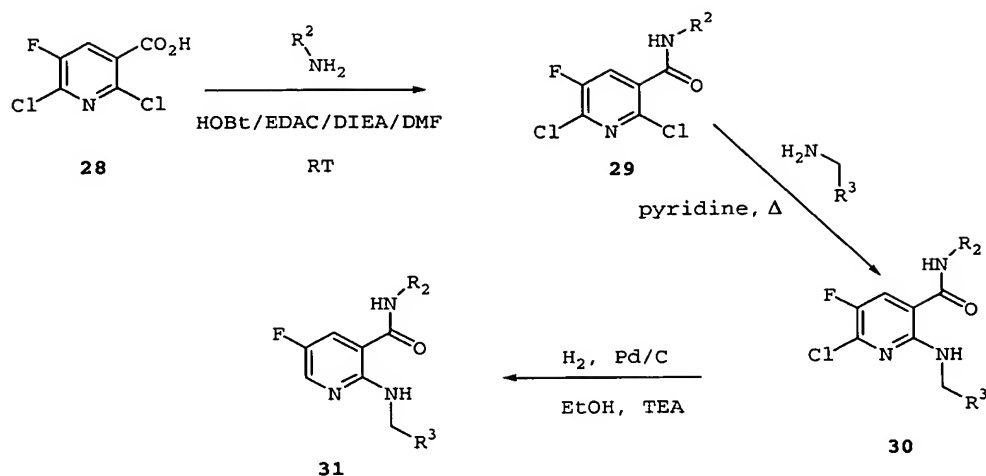
phosphite, such as diethylchlorophosphite, 1,2-phenylene chlorophosphite, ethyldichlorophosphite, ethylene chlorophosphite or tetraethylpyrophosphite. A derivative of such a compound having an amino group also can be a carbamic acid halide or an isocyanate.

The condensation of activated sulfonic esters, reactive anhydrides or reactive cyclic amides with the corresponding amines is customarily carried out in the presence of an inorganic base, such as an alkaline metal hydrogen carbonate or carbonate, or especially an organic base, for example simple lower (alkyl)₃-amines, for example TEA or tributylamine, or one of the above-mentioned organic bases. If desired, a condensation agent is additionally used, for example as described for free carboxylic acids.

The condensation is preferably carried out in an inert, aprotic, preferably anhydrous, solvent or solvent mixture, for example in a carboxylic acid amide, for example formamide or DMF, a halogenated hydrocarbon, for example CH₂Cl₂, CCl₄ or chlorobenzene, a ketone, for example acetone, a cyclic ether, for example THF or dioxane, an ester, for example EtOAc, or a nitrile, for example CH₃CN, or in a mixture thereof, as appropriate at reduced or elevated temperature, for example in a temperature range of from about -40 °C to about 100 °C, preferably from about -10 °C to about 70 °C, and when arylsulfonyl esters are used also at temperatures of from about 10-30 °C, and if necessary under an inert gas atmosphere, for example a nitrogen or argon atmosphere.

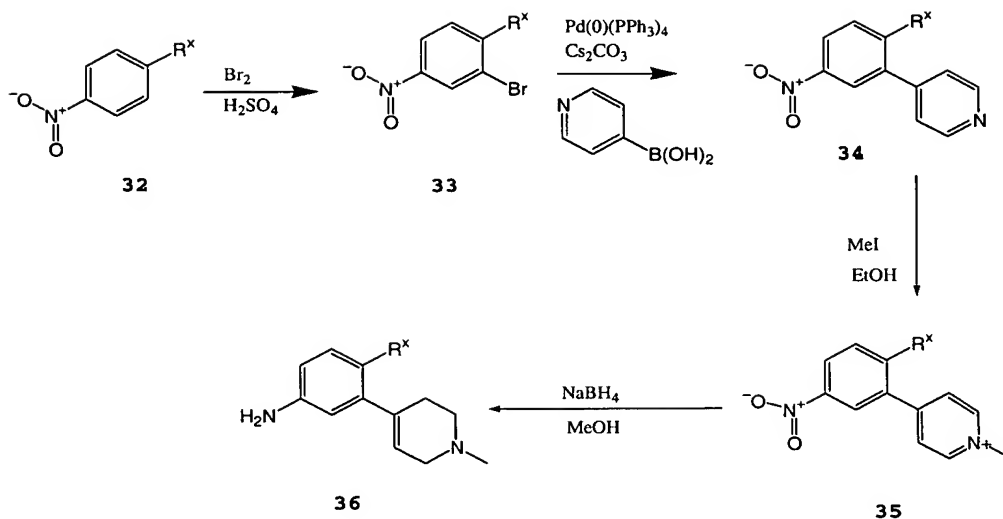
Alcoholic solvents, for example EtOH, or aromatic solvents, for example benzene or toluene, may also be used. When alkali metal hydroxides are present as bases, acetone may also be added where appropriate.

Scheme 14



5 Substituted pyridines can be prepared by the process
outlined in Scheme 14. 2-Chloronicotinic acid **28** and
substituted amine are coupled under conditions similar to
that described in the previous schemes to give the amide **29**.
6-Chloro-2-aminopyridines **30** are prepared from the amide **29**,
10 such as by reacting with substituted amines at a suitable
temperature, such as above about 80 °C, preferably above
about 100 °C, more preferably at about 130 °C, neat. 6-
Chloro-2-aminopyridines **30** are de-chlorinated such as by
hydrogenation, for example by treatment with H₂ in the
15 presence of Pd/C, to yield other compounds of the present
invention **31**.

Scheme 15

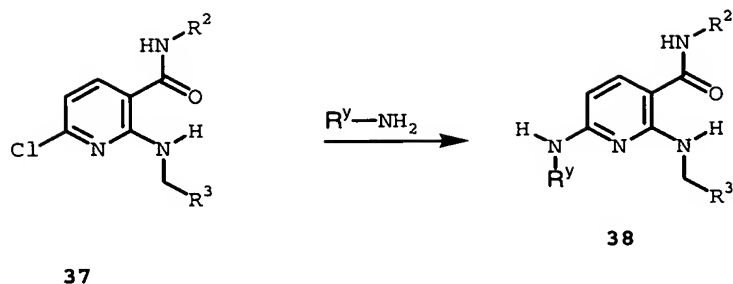


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1,2,3,6-Tetrahydropyridyl substituted anilines (where R^x is a substituent selected from those available for substituted R^2) are prepared such as by the procedure described in Scheme 15. Nitrobenzenes **32** are brominated, such as with bromine in the presence of acid, H_2SO_4 for example, or with NBS to yield the 3-bromo derivative **33**. Suzuki coupling of the bromo-derivative **33** and a substituted pyridylboronic acid, such as at a temperature above RT, preferably above about $50\text{ }^\circ\text{C}$, and more preferably at about $80\text{ }^\circ\text{C}$, yields the pyridyl derivative **34**. Alkylation of the nitrophenyl-pyridine **34**, such as by treatment with iodomethane, preferably above about $50\text{ }^\circ\text{C}$, and more preferably at about $80\text{ }^\circ\text{C}$, yields the pyridinium compound **35**, which upon reduction, such as by NaBH_4 , yields the tetrahydropyridine **36**.

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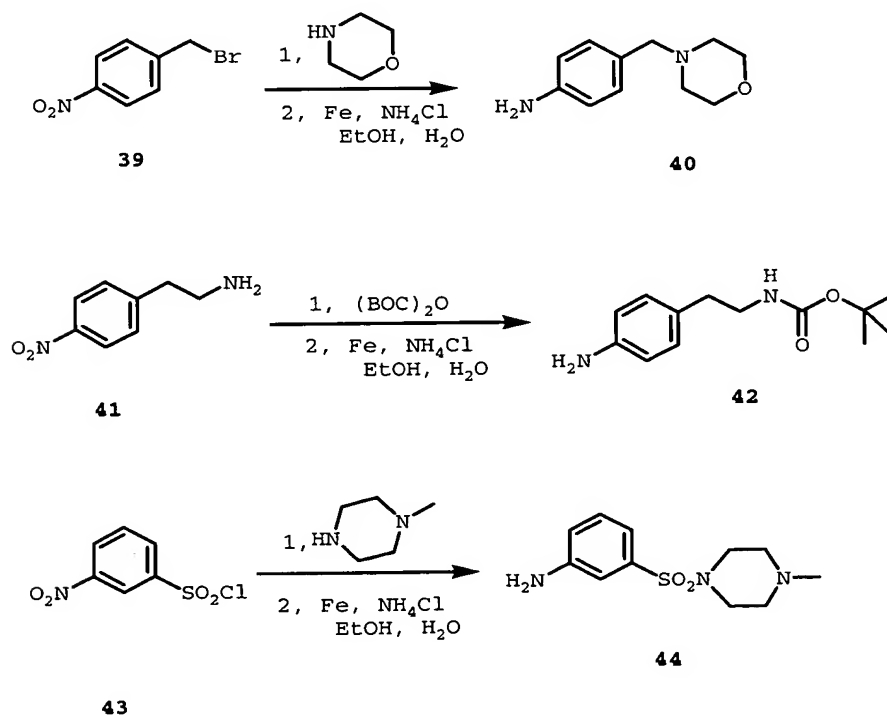
Scheme 16



5

6-Amino substituted pyridines are prepared such as by the procedure described in Scheme 16. Similar to the method of Scheme 13, chloropyridine **37** and is reacted with an amine, preferably above about 50 °C, and more preferably at about 80 °C, to yield the 6-aminopyridines **38**.

Scheme 17

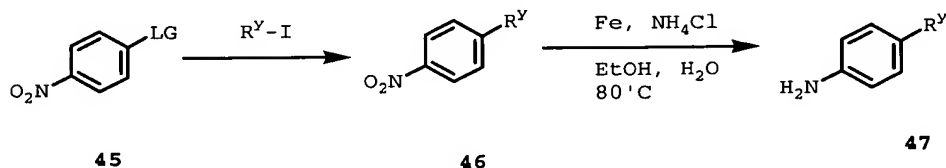


A series of substituted anilines are prepared such as by the procedure described in Scheme 17. A nitrobenzyl bromide **39** is coupled with morpholine, such as at a temperature at about RT, to yield the heterocyclylmethyl nitrobenzene derivative. Reduction of the nitro compound, such as with iron powder, preferably above about 50 °C, and more preferably at about 80 °C, yields the heterocyclylmethyl substituted aniline **40**.

Protected alkylamine substituted anilines can be prepared from the nitro free amines **41**, such as with standard protecting agents and chemistry known in the art, such as BOC chemistry. Reduction of the protected nitro compound, such as with iron powder, preferably above about 50 °C, and more preferably at about 80 °C, yields the aniline **42**.

Sulfonamide substituted anilines can be prepared from nitrobenzenesulfonyl chlorides **43**. Coupling of nitrobenzenesulfonyl chlorides **43** with reactive heterocyclic compounds, such as substituted piperazines, piperidines, and the like, in a protic solvent such as EtOH, such as at a temperature about RT, yields the nitrobenzenesulfonamides **43**. Reduction of the nitro benzenesulfonamide, such as with iron powder, preferably above about 50 °C, and more preferably at about 80 °C, yields the aniline **44**.

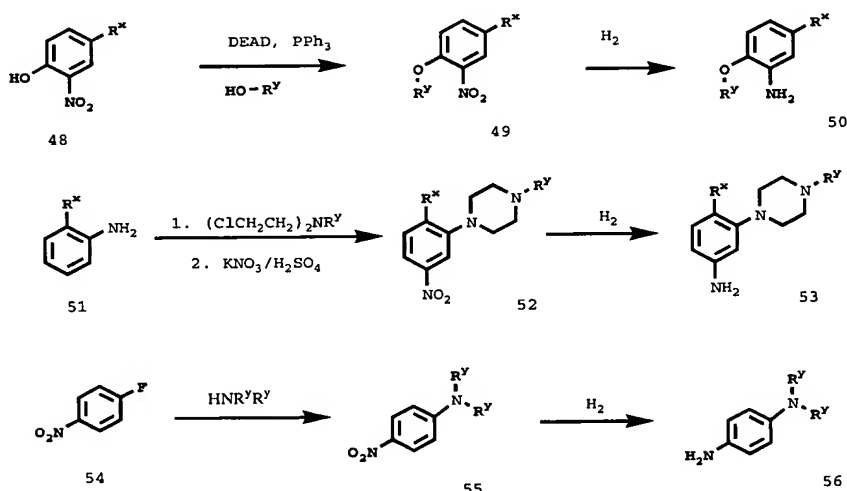
Scheme 18



A series of perhaloalkyl-substituted anilines **47**, where R^Y represents perhaloalkyl radicals, are prepared such as by the procedure described in Scheme 18. 1-Nitro-4-(perfluoroethyl)benzene can be synthesized by the method described in the reference [John N. Freskos, Synthetic Communications, 18(9):965-972 (1988)]. Alternatively, 1-Nitro-4-(perfluoroalkyl)benzene can be synthesized from the nitro compound, where LG is a leaving group, such as iodo, by the method described by W. A. Gregory, et al. [J. Med. Chem., 33:2569-2578 (1990)].

Reduction of the nitrobenzenes **46**, such as with iron powder, at a temperature above about 50 °C, and preferably at about 80 °C, yields the aniline **47**. Hydrogenation, such as with H_2 atmosphere in the presence of catalyst, such as 10% Pd/C, is also possible.

Scheme 19



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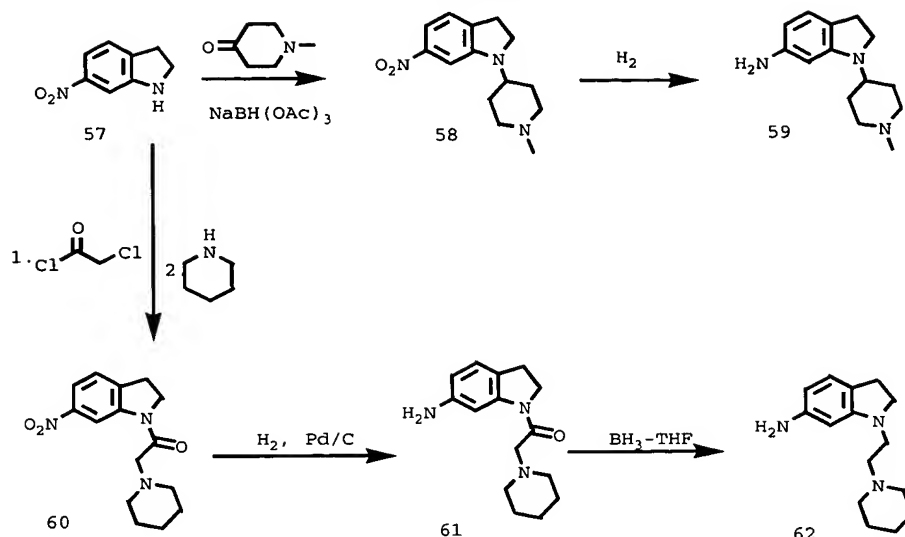
Additional series of substituted anilines (where R^X is a substituent selected those available for substituted R^2) - are prepared such as by the procedures described in Scheme 19. 2-Alkoxy substituted anilines **50** are prepared from the

corresponding phenol compounds **48** such as by the Mitsunobu reaction, including treatment with a N,N-dialkylethanolamine and PPh₃ and DEAD to give the corresponding nitro compound **49**, followed by hydrogenation, such as with H₂ to give the aniline **50**.

Alternatively, piperazinyl substituted anilines **53** can be prepared by the treatment of an aniline **51** with an N-substituted-bis(2-chloroethyl)amine, base, such as K₂CO₃ and NaI, at a temperature above about 50 °C, preferably above about 100 °C, and more preferably at about 170 °C, to give the piperazinylbenzene compound **52**. Nitration, such as with H₂SO₄ and KNO₃, at a temperature above 0 °C, and preferably at about RT, followed by hydrogenation, such as with H₂ atmosphere gives the substituted aniline **53**.

Alternatively, piperazinyl substituted anilines **56** can be prepared by the treatment of a fluoro-nitro-substituted aryl compounds **54**. The fluoro-nitro-substituted aryl compounds **54** and 1-substituted piperazines are heated, preferably neat, at a temperature above about 50 °C, and preferably at about 90 °C, to yield the piperazinyl-nitroaryl compounds **55**. Hydrogenation, such as with H₂ atmosphere in the presence of a catalyst, such as 10% Pd/C, gives the substituted aniline **56**.

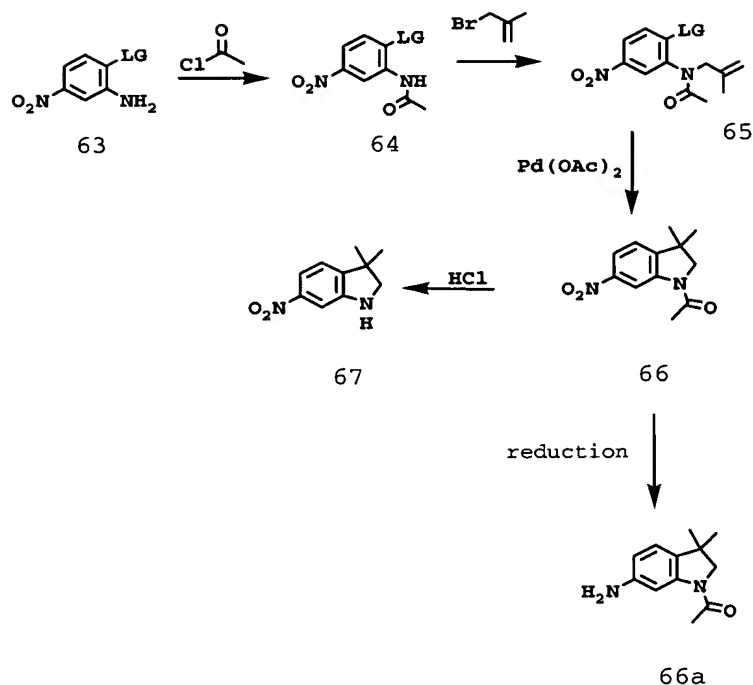
Scheme 20



Substituted indolines are prepared such as by the
 5 procedures described in Scheme 20. Substituted amino-
 indolines **59** are prepared from the nitroindoline **57** and a
 ketone in the presence of $\text{NaHB}(\text{OAc})_3$ to form the 1-
 substituted indoline **58**. The nitroindoline **58** is
 hydrogenated, such as with H_2 in the presence of a catalyst,
 10 such as Pd/C , to yield the amino-indoline **59**.

Alternatively, substituted amino-indolines **62** are
 prepared from the nitroindoline **57**. Nitroindoline **57**, is
 reacted with an acid chloride to form an amide. Further
 treatment with a primary or secondary amine, preferably a
 15 secondary amine, such as in the presence of NaI , at a
 temperature above about 50°C , and preferably at about 70°C
 yields the nitroindoline **60**. The nitro compound **60** is
 hydrogenated, such as with H_2 in the presence of a catalyst,
 such as Pd/C , to yield the amino-indoline **61**. The carbonyl
 20 is reduced, such as with BH_3 -THF, to yield 1-aminoalkyl-
 indolines **62**.

Scheme 21



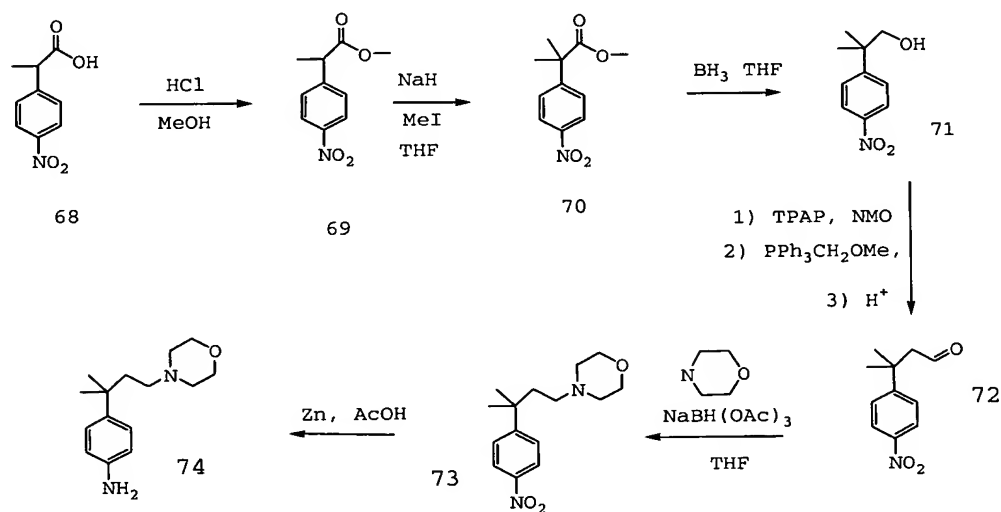
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Substituted indolines are prepared such as by the procedures described in Scheme 21. Substituted acetamides **64** are prepared from the coupling of halo-5-nitroanilines **63** (where LG is bromo or chloro, preferably chloro) and an acylating agent, such as acetyl chloride or acetic anhydride, under standard coupling chemistry, such as with DIEA, and DMAP, at a temperature of about RT, in a suitable solvent, such as CH_2Cl_2 , DMF and/or DMAC. The N-(2-methylprop-2-enyl)acetamide **65** is prepared from the acetamide **64**, such as by the treatment of base, such as NaH in a suitable solvent such as NMP or anhydrous DMF and a 3-halo-2-methylpropene such as 3-bromo-2-methylpropene or 3-chloro-2-methylpropene, at a temperature between about 0 °C and RT, and preferably at about RT; or with CsCO_3 at a temperature above RT, preferably above about 50 °C and more

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preferably above about 60 °C. Cyclization of the N-(2-methylprop-2-enyl)acetamide **65**, such as by the Heck-type reaction (treatment with Pd(OAc)₂ in the presence of base, for example tetraethyl-ammonium chloride, sodium formate, and NaOAc) at a temperature above about 50 °C, and preferably at about 80°C, yields the protected (3,3-dimethyl-2,3-dihydro-indol-1-yl)ethanone **66**. Deprotection, such as with strong acid such as AcOH, or HCl at a temperature above about 50 °C, and preferably at about 70-80 °C, yields the 3,3-dimethyl-6-nitro-2,3-dihydro-indol-1-yl **67**. Alternatively, the protected dihydro-6-nitro indoline **66** can be reduced, such as with Fe, or with 10% Pd/C in the presence of an excess of NH₄CO₂H, or with H₂ in the presence of a catalyst to form the protected dihydro-6-amino indoline **66a**.

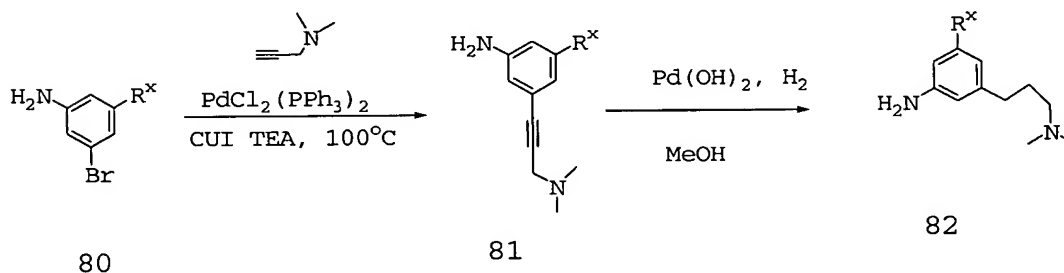
Scheme 22



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Substituted anilines are prepared such as by the procedures described in Scheme 22. Nitrophenyl esters **69** are formed from the acid **68**, such as by treatment with MeOH and acid. Alkylation of the ester **69**, such as by treatment

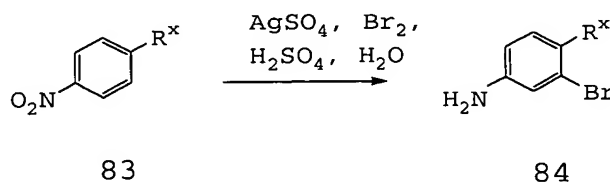
with base, such as NaH, followed by alkyl halide, yields the branched alkyl compounds **70**. Reduction of the ester **70**, such as with BH_3 , yields the alcohol **71**. The aldehyde **72** is prepared from the alcohol **71**, such as by treatment with TPAP in the presence of N-methylmorpholine-N-oxide. Subsequent treatment with methoxymethyltriphenylphosphonium chloride and KHMDS yields **72**. Coupling of the aldehyde **72** with morpholine, such as with $\text{NaBH}(\text{OAc})_3$, yields the tertiary amine **73**. Reduction of the nitro compound, such as with acid, for example AcOH, and zinc yields the aniline **74**.

Scheme 23

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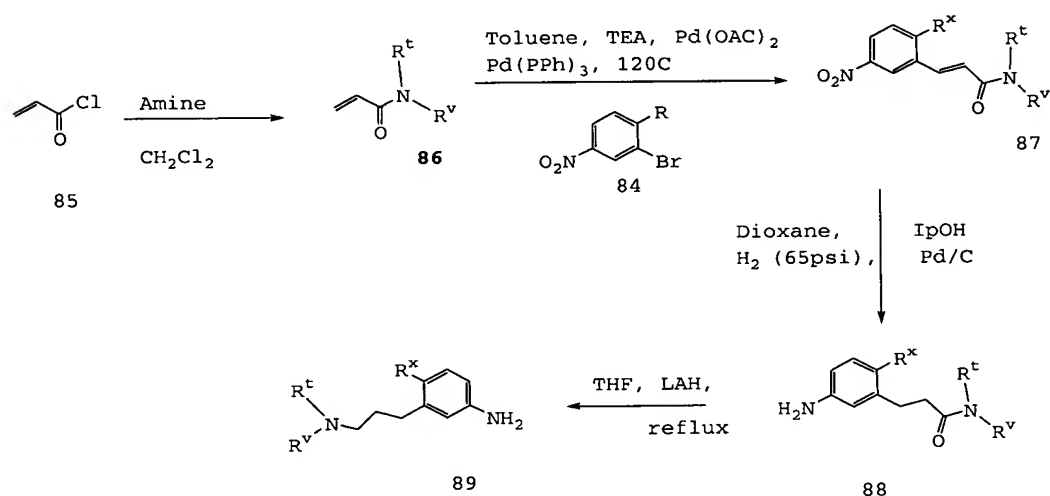
Substituted aniline compounds (where R^x is a substituent selected those available for substituted R^2 , preferably haloalkyl and alkyl) are prepared such as by the procedure described in Scheme 23. Alkynyl-aniline **81**, prepared similar to that described in Scheme 23, is hydrogenated such as with H_2 in the presence of a catalyst, such as $\text{Pd}(\text{OH})_2$, to yield the substituted alkyl **82**.

25

Scheme 24

Substituted bromophenyl compounds are prepared such as by the procedure described in Scheme 24. Bromine is added to an optionally substituted nitrobenzene **83**, AgSO₄ and acid, such as H₂SO₄, to provide the bromo derivative **84**.

Scheme 25



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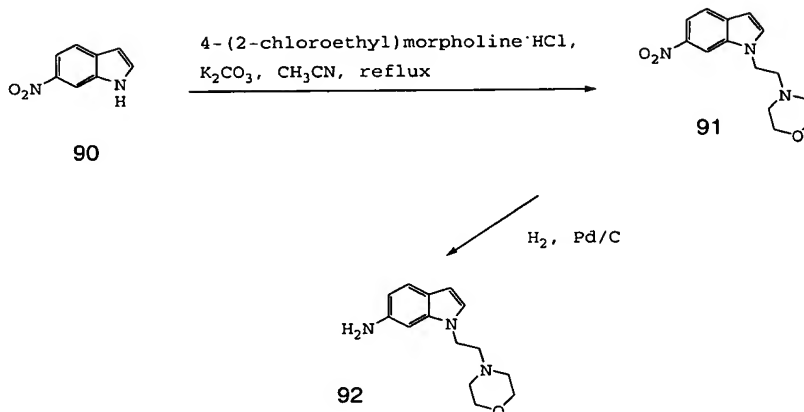
Substituted anilines are prepared such as by the procedure described in Scheme 25 (where R^t and R^v are alkyl, or together with the nitrogen atom form a 4-6 membered heterocyclic ring). Acryloyl chloride **85** is reacted with an amine, preferably a secondary amine, such as at a temperature between about 0 °C and about RT, to form the amide **86**. A bromo-nitrobenzene **84** is reacted with the amide **88**, such as in the presence of base, for example TEA, together with Pd(OAc)₂ and Pd(PPh₃)₄, at a temperature above about 50 °C, and preferably at about 120 °C, such as in a sealed container, to form the substituted alkene **87**. Hydrogenation of the alkene **87**, such as with H₂ in the presence of a catalyst, for example Pd/C catalyst yields the substituted aniline **88**. Reduction of the amide **88**, such as

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with LiAlH_4 , at a temperature above about 50°C , and preferably at about 80°C yields the aniline **89**.

Scheme 26

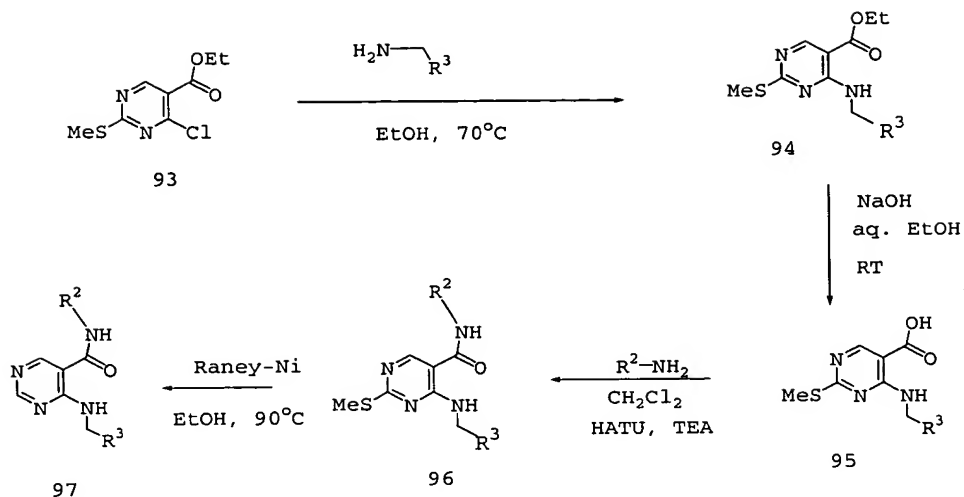
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Substituted indoles are prepared such as by the procedure described in Scheme 26. A nitroindole **90** is coupled with a halo compound, in the presence of base, for example K_2CO_3 . Heating at a temperature above about 50°C , and preferably at about reflux yields the substituted-nitro-1H-indole **91**. Hydrogenation similar to conditions described above yields the amino derivative **92**.

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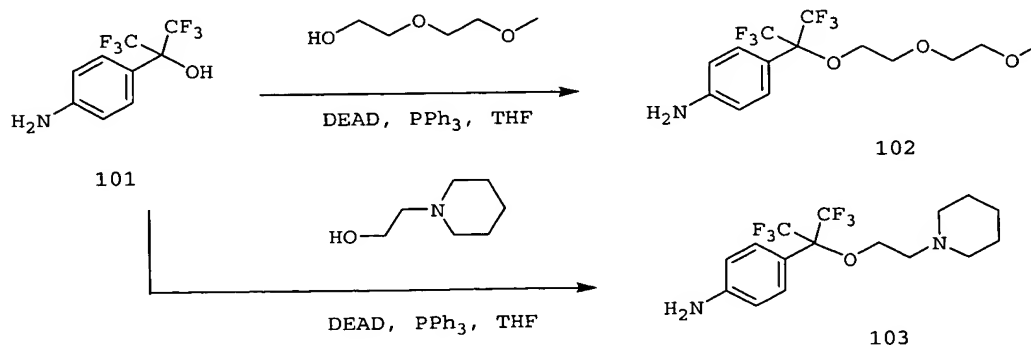
Scheme 27



5 Substituted pyrimidines are prepared such as by the
 procedure described in Scheme 27. 2-Methylthio-5-pyrimidyl
 acids **95** are prepared from the corresponding esters **93**
 similar to procedures described above. The amides **96** are
 formed from the acids **95** by coupling with the amine such as
 10 in the presence of HATU and base, TEA for example. The
 methylthio group can be removed, such as with Raney-Ni and
 heat, preferably at about reflux temperature, to form the
 pyrimidine **97**.

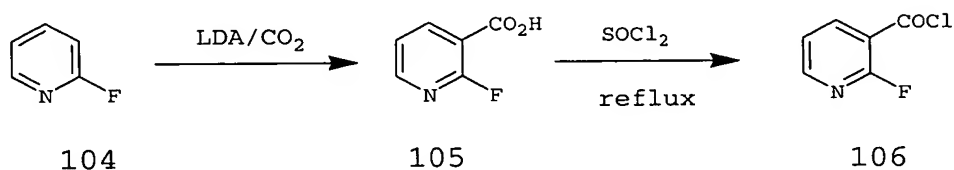
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Scheme 28



Substituted anilines are prepared such as by the procedure described in Scheme 28. Treatment with the haloalkyl alcohol **101** with an alcohol, such as in the presence of DEAD and PPh₃, yields the ether **102** or **103**.

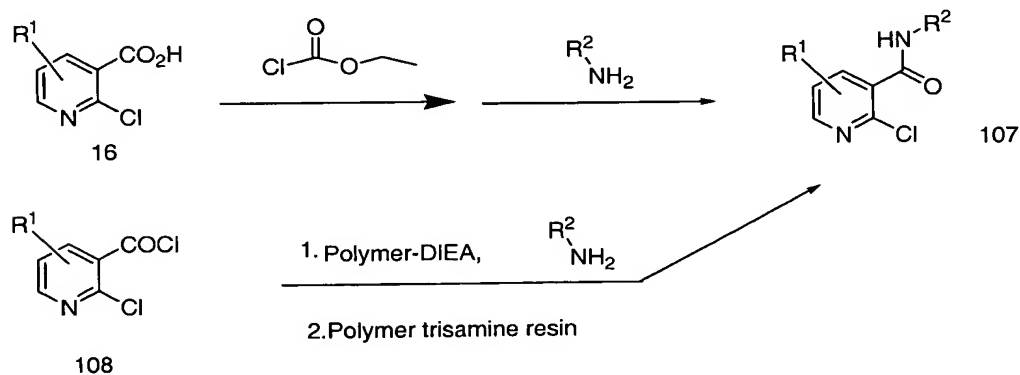
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Scheme 29

10 Functionalized pyridines are prepared such as by the procedure described in Scheme 29. 2-Fluoropyridine **104** is treated with base, such as LDA, at a temperature below about 0 °C, and preferably at about -78 °C, and quenched with a stream of dry CO₂ to form the nicotinic acid **105**.

15 Alternatively, solid CO₂ (dry ice) can be used, preferably dried with N₂ prior to use. The acid **105** is converted to the acid halide **106**, such as by treatment with thionyl chloride and heating at a temperature above about 50 °C, and preferably at about reflux.

20

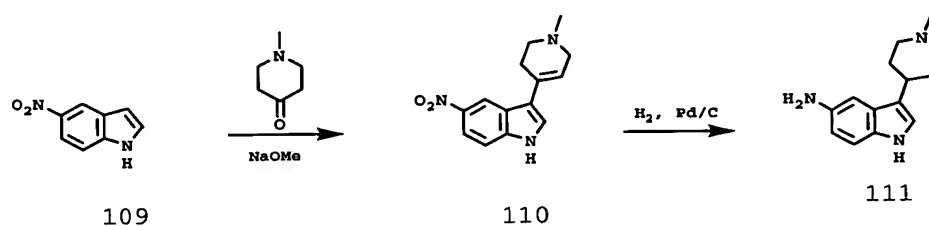
Scheme 30

Chloro-substituted pyridines **107** are prepared such as by the procedure described in Scheme 30. 2-Chloronicotinic acid is activated with ethyl chloroformate, in the presence of base, such as TEA, at a temperature of about RT.

- 5 Reaction with an amine produces amide **107**. Alternatively, the amine can be coupled with the acid chloride **108**, such as with polymer-supported DIEA. Excess acid chloride is removed by treating the reaction mixture with polymer-supported trisamine resin, to form amide **107**.

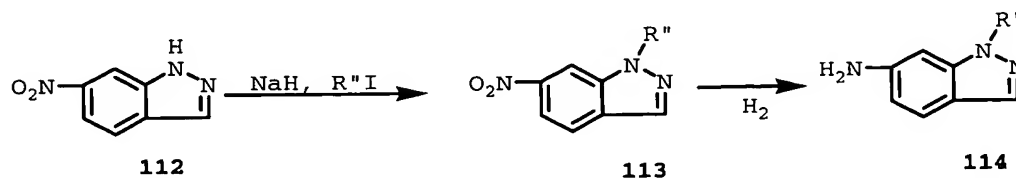
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Scheme 31



- 15 Amino-substituted indoles **111** are prepared such as by the procedure described in Scheme 31. Nitroindoline **109** is reacted with N-methyl-4-piperidone in the presence of NaOMe at a temperature above about 50 °C, and preferably at about reflux, to form the 3-substituted indole **110**. Hydrogenation
20 as previously discussed yields the amino indole **111**.

Scheme 32

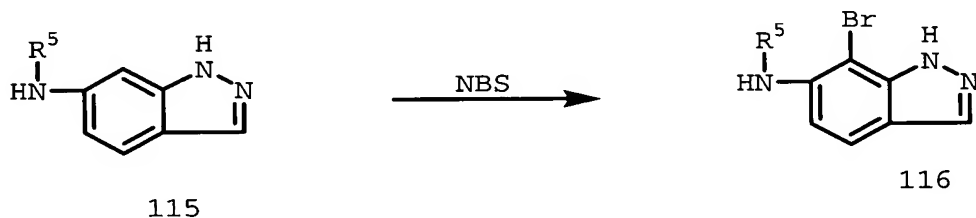


25

Alkylated indazoles can be prepared by the process outlined in Scheme 32. To a solution of 6-nitroindazole **112**

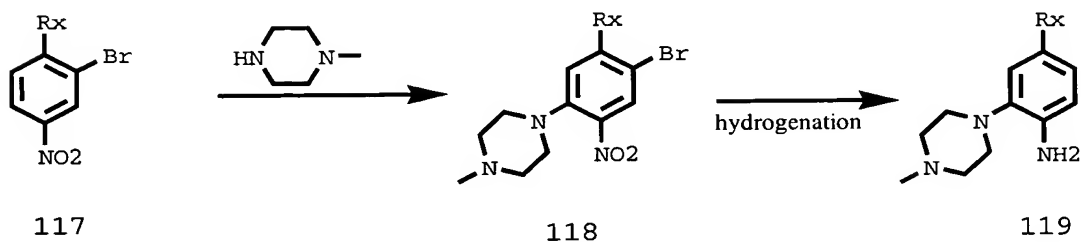
in a solvent such as THF is added strong base, such as NaH at a temperature below RT, preferably at about 0 °C. Alkylhalides, such as where R" is methyl, are added and reacted at a temperature about RT to give 1-alkyl-6-nitro-1H-indazole **113**. The nitro indazole **113** is hydrogenated, such as with an H₂ atmosphere in the presence of a catalyst, such as Pd/C to give the 1-substituted-6-amino-1H-indazole **114**.

10

Scheme 33

Brominated indazoles can be prepared by the process outlined in Scheme 33. NBS is slowly added to an acidic solution, such as a mixture of TFA:H₂SO₄ (5:1) and *tert*-butyl-4-nitrobenzene **115** at a temperature of about RT to yield the brominated compound **116**.

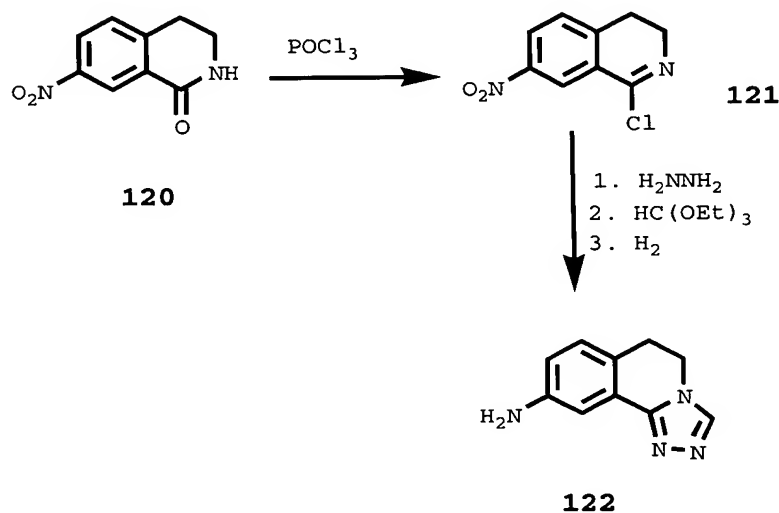
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Scheme 34

Substituted anilines (where R^x is a substituent selected those available for substituted R²) can be prepared by the process outlined in Scheme 34. A mixture of 1-

(substituted)-2-bromo-4-nitrobenzene **117** and N-methylpiperazine is heated, such as with or without solvent, preferably without solvent, at a temperature above RT, preferably at a temperature above about 100 °C, and more preferably at a temperature at about 130 °C to give the 1-[5-(substituted)-2-nitrophenyl]-4-methylpiperazine **118**. The nitro compound **118** is hydrogenated, such as with an H₂ atmosphere in the presence of a catalyst, such as Pd/C to furnish 4-(substituted)-2-(4-methylpiperaziny)phenylamine **119**.

Scheme 35

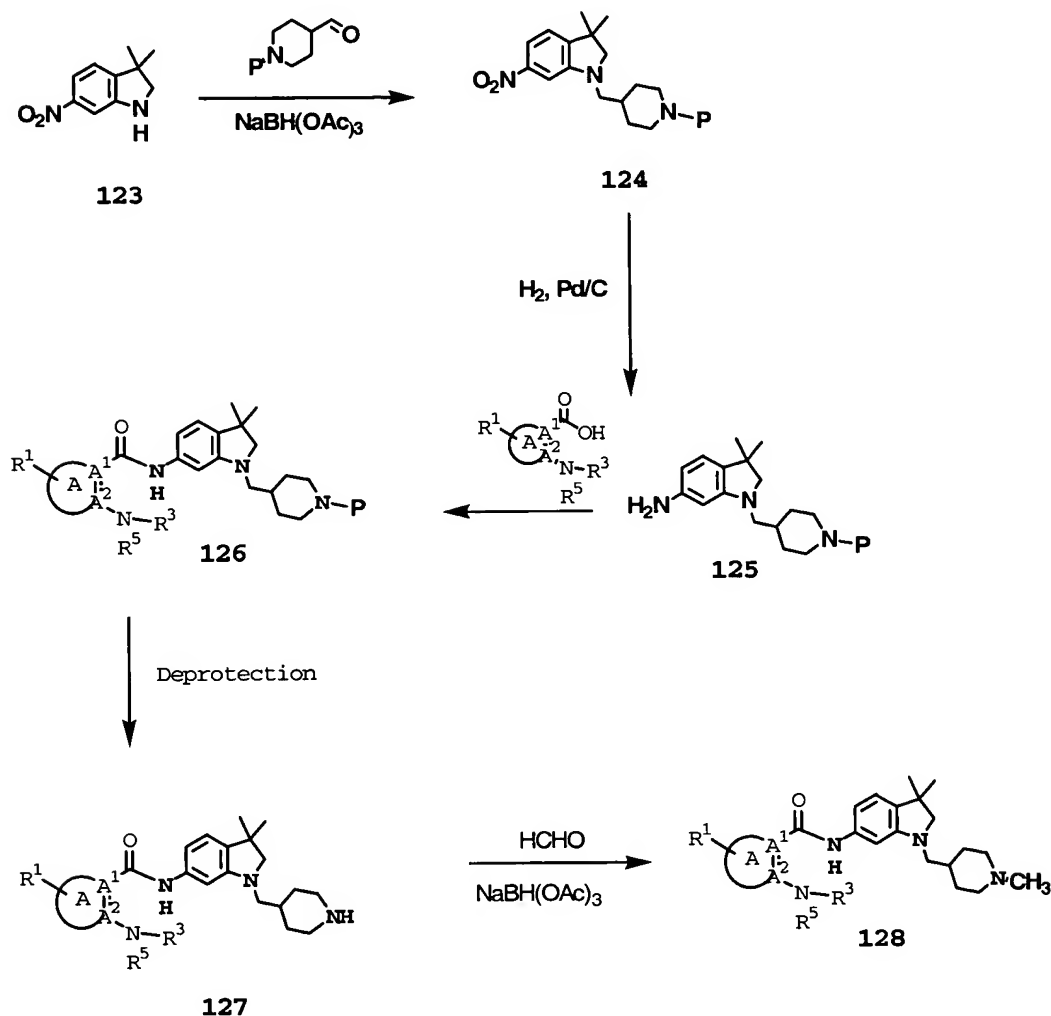


Tricyclic heterocycles can be prepared by the process outlined in Scheme 35. 7-Nitro-2,3,4-trihydroisoquinolin-1-one **120** is heated in POCl₃ at a temperature above RT, preferably at a temperature sufficient for reflux, to form the 1-chloro-7-nitro-3,4-dihydroisoquinoline **121**. The 1-chloro-7-nitro-3,4-dihydroisoquinoline **121** is dissolved in a solvent, such as THF, and H₂NNH₂ is added. The reaction is heated with HC(OEt)₃ at a temperature above RT, preferably at a temperature above about 75 °C, and more preferably at a temperature at about 115 °C to give the nitro-substituted

tricyclic. Hydrogenation, such as with an H₂ atmosphere in the presence of a catalyst, such as Pd/C, gives 2-amino-5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinoline **122**.

5

Scheme 36

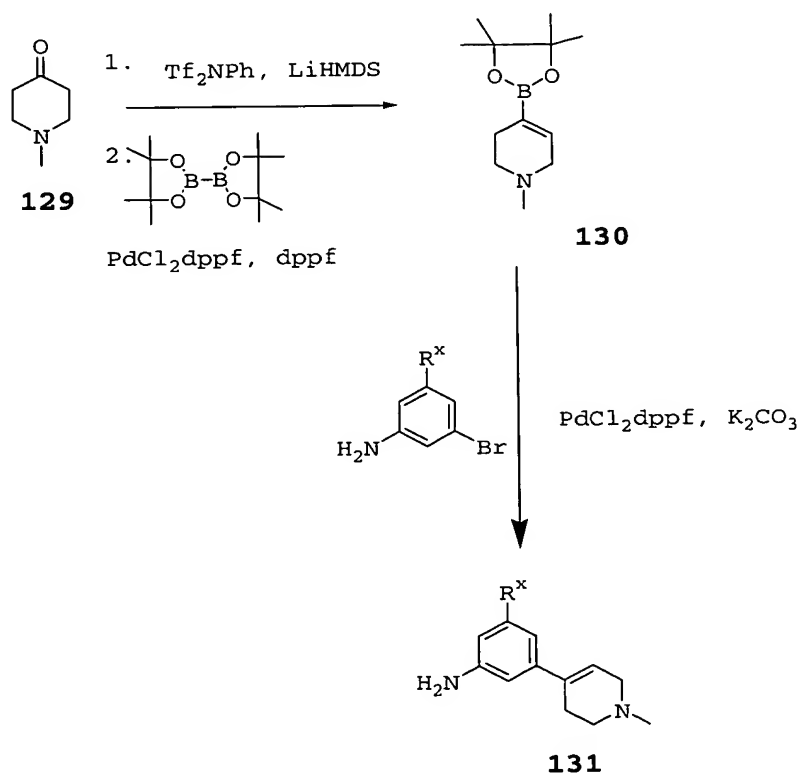


Indolyl substituted carboxamides can be prepared from the corresponding nitro indoline **123** by the process outlined in Scheme 36. For example, 3,3-dimethyl-6-nitroindoline **123** is alkylated, such as with N-protected-4-formylpiperidine in the presence of NaBH(OAc)₃ and acid,

10

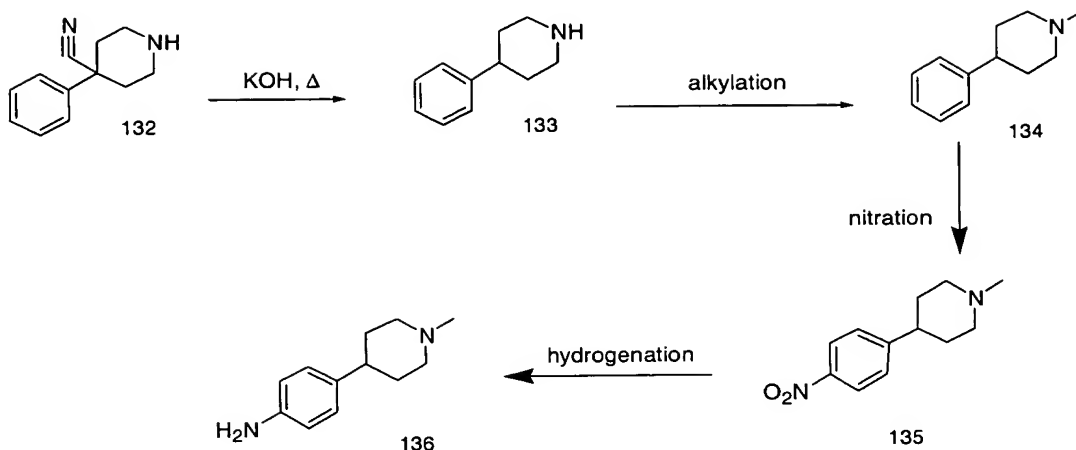
such as glacial AcOH, and solvent, such as dichloromethane, at a temperature of about RT, to afford the alkylated indane **124**. Hydrogenation of the alkylated indane **124**, such as with an H₂ atmosphere in the presence of a catalyst, such as Pd/C, in the presence of a solvent, such as an alcohol, preferably MeOH, to give the amino intermediate **125**.
Alternatively, other hydrogenation methods can be used, such as Fe powder with NH₄Cl. Coupling of the amine **125**, such as with 2-chloronicotinic acid and DIEA, HOBt and EDC, in a solvent such as CH₂Cl₂ at a temperature of about RT provides the protected carboxamide **126**, which upon deprotection and alkylation yields other compounds of the invention, **127** and **128**, respectively. Alternatively, amine **125** is reacted with 2-fluoronicotinoyl chloride to form a 2-fluoronicotinamide, which can be alkylated, such as in Scheme 10.

Scheme 37



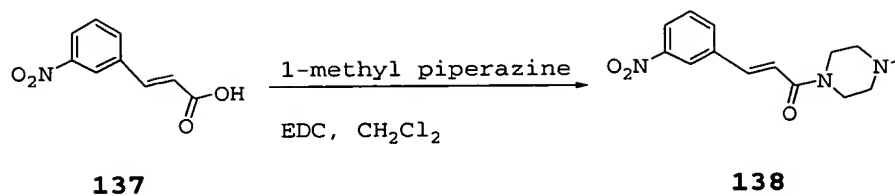
Substituted anilines can be prepared by the process outlined in Scheme 37 (where R^x is a substituent selected those available for substituted R², preferably haloalkyl and alkyl). 1-Methyl-4-piperidinone **129** is added to a solution of strong base such as LiHMDS, in a solvent such as THF, at a temperature below RT, preferably lower than about -50 °C, more preferably at about -78 °C. Tf₂NPh is reacted with the enolate at a temperature of about RT, to give 1-methyl-4-(1,2,5,6-tetrahydro)pyridyl-(trifluoromethyl)sulfonate. A mixture of the triflate intermediate, bis(pinacolato) diboron, potassium acetate, PdCl₂dppf, and dppf in a solvent such as dioxane is heated at a temperature above RT, preferably at a temperature above about 50 °C, and more preferably at a temperature at about 80 °C to give 4,4,5,5-tetramethyl-2-(1-methyl(4-1,2,5,6-tetrahydropyridyl))-1,3,2-dioxaborolane **130**. The substituted aniline **131** is formed from the 1,3,2-dioxaborolane **130** such as with treatment with an amine in the presence of PdCl₂dppf and base, such as K₂CO₃, in a solvent such as DMF at a temperature above RT, preferably at a temperature above about 50 °C, and more preferably at a temperature at about 80 °C.

Scheme 38



- 5 Substituted anilines can be prepared by the process
outlined in Scheme 38. 4-Cyano-4-phenylpiperidine
hydrochloride **132** is treated with base, such as KOH, at a
temperature above RT, preferably at a temperature above
about 100 °C, and more preferably at a temperature at about
10 160 °C, to provide the phenyl piperidine **133**. Alkylation of
the phenyl piperidine **133**, such as with formaldehyde and
NaCNBH₃ in a solvent such as CH₃CN, with sufficient acid to
maintain the reaction pH near 7, to provide the alkylated
piperidine **134**. Nitration of the phenylpiperidine **134**, such
15 as with H₂SO₄ and fuming HNO₃ at a temperature below RT, and
preferably at about 0 °C, gives the nitro intermediate **135**.
Hydrogenation of the nitro intermediate **135**, such as with an
H₂ atmosphere in the presence of a catalyst, such as Pd/C,
in the presence of a solvent, such as an alcohol, preferably
20 MeOH, to give the amino intermediate **136**.

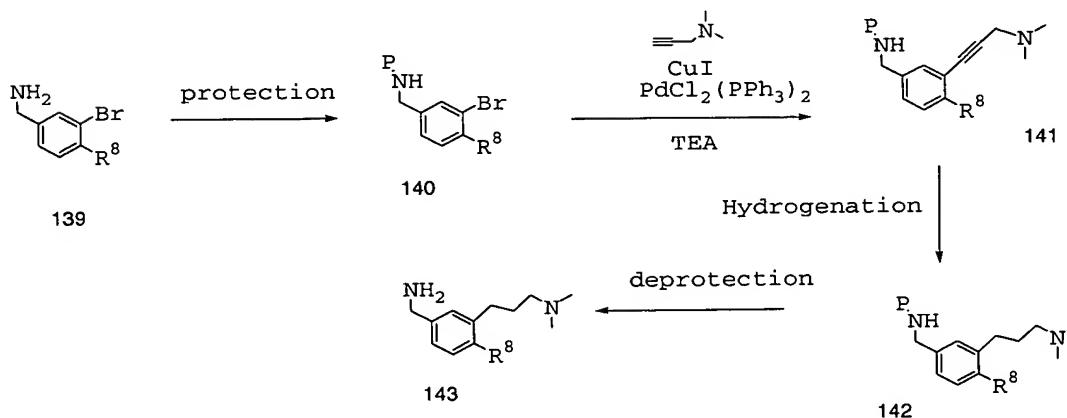
Scheme 39



5 Substituted amides can be prepared by the process outlined in Scheme 39. 3-Nitrocinnamic acid **137** is coupled with 1-methylpiperazine in the presence of EDC and a solvent such as CH₂Cl₂, at a temperature of about RT gives the carboxamide **138**.

10

Scheme 40

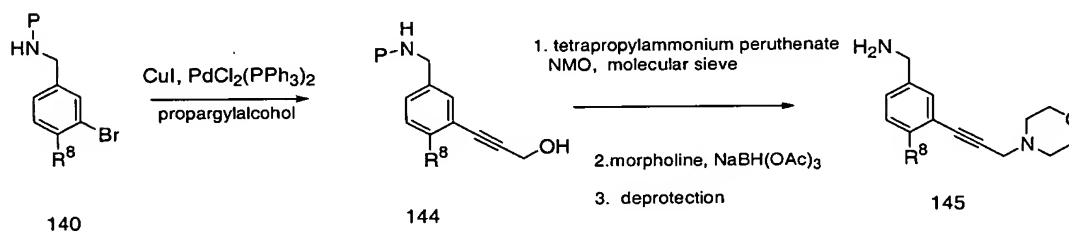


15 Substituted benzylamines can be prepared by the process outlined in Scheme 40. A substituted bromobenzylamine **139** where R^{2a} is a substituent described for R² is protected such as with Boc₂O in the presence of base, such as TEA in an appropriate solvent such as CH₂Cl₂.

20 The protected bromobenzylamine **140** is alkylated, such as with 1-dimethylamino-2-propyne in the presence of catalyst, such as PdCl₂(PPh₃)₂ bis(triphenylphosphino)-palladium chloride, and CuI, in the presence of base, such as TEA, at

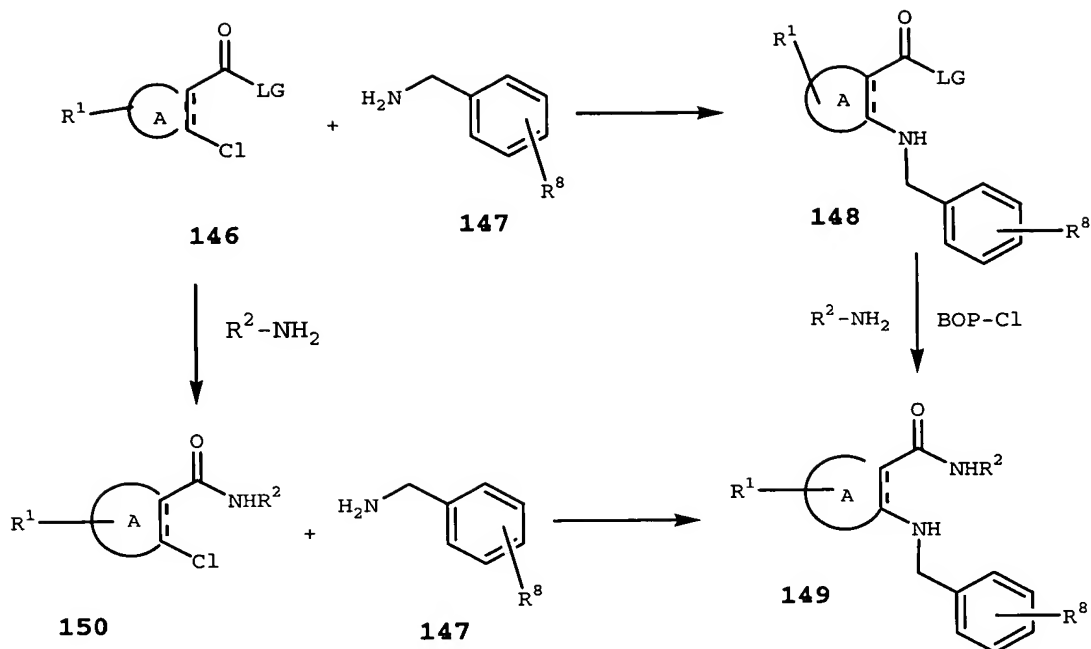
a temperature above RT, preferably at a temperature above about 50 °C, and more preferably at a temperature at about 100 °C, such as in a sealed tube, to form the propynylbenzylamine **141**. The propynylbenzylamine is hydrogenated such as with H₂ in the presence of Pd(OH)₂ and MeOH to provide the propylbenzylamine **142**. Deprotection, such as with strong acid, such as TFA, for removal of a Boc protecting group, yields the propylbenzylamine **143**.

10

Scheme 41

Substituted benzylamines can be prepared by the process outlined in Scheme 41. The protected bromobenzylamine **140** is alkylated, such as with propargyl alcohol in the presence of catalyst, such as PdCl₂(PPh₃), and CuI, in the presence of base, such as TEA, at a temperature above RT, preferably at a temperature above about 50 °C, and more preferably at a temperature at about 100 °C, such as in a sealed tube, to form the protected hydroxypropynylbenzylamine **144**. The protected hydroxypropynylbenzylamine is treated with N-methylmorpholine oxide in the presence of a catalyst, such as tetrapropylammonium perruthenate, to form the aldehyde intermediate. Reductive amination, such as with the addition of morpholine and NaBH(OAc)₃ provides the morpholinyl derivative. Deprotection, such as with strong acid, such as TFA, for removal of a Boc protecting group, yields the propylbenzylamine **145**.

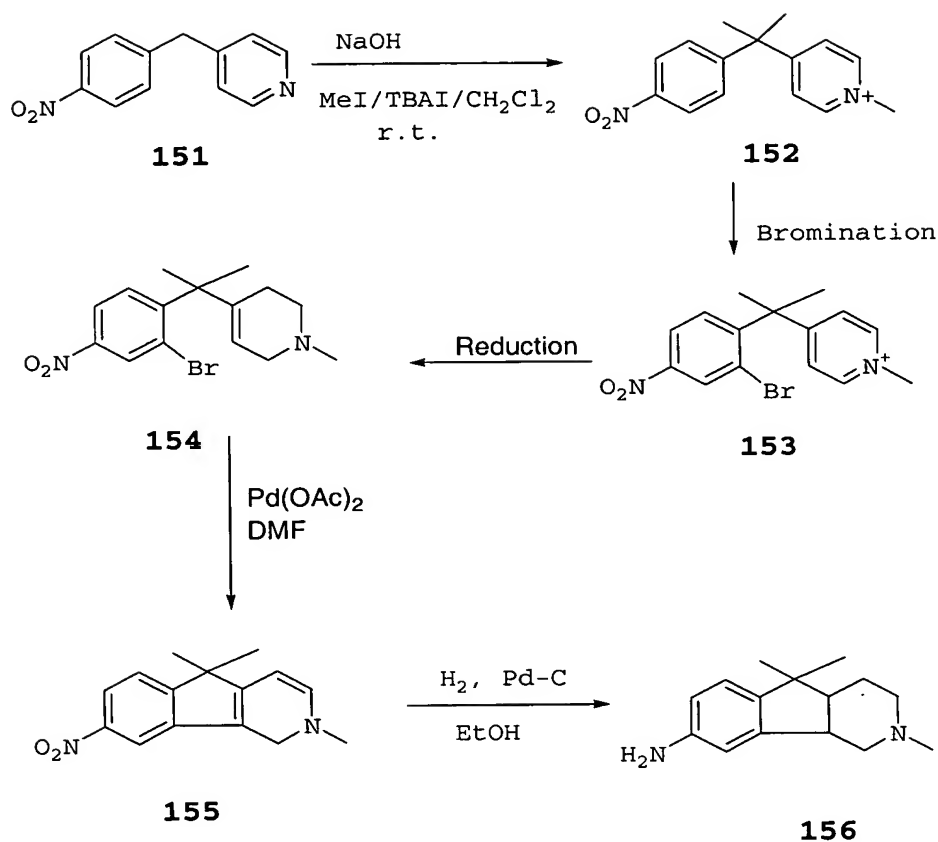
Scheme 42



5 Substituted heterocycles may be prepared by the method found in Scheme 42. Chloro-heterocycles **146** (where LG is OH) is coupled with an amine **147** at a suitable temperature, such as a temperature over about 100 °C to give the 2-substituted amino-nicotinic acid **148**. The 2-substituted amino-nicotinic
 10 acid **148** is reacted with a substituted amine in the presence of a coupling reagent, such as BOP-Cl and base, such as TEA to form the 2-substituted amino-nicotinamide **149**.

 Alternatively, 2-chloro-nicotinoyl chloride **146** (where LG is Cl) is coupled first with R^2-NH_2 , such as in the
 15 presence of base, e.g., $NaHCO_3$, in a suitable solvent, such as IpOH or CH_2Cl_2 , to form the amide **150**, then coupled with a benzylamine **147** to yield the 2-substituted amino-nicotinamide **149**. Where A is a pi-electron rich heterocycle, the addition of KF, such as 40% KF on alumina
 20 in IpOH, at a temperature over about 100 °C, preferably about 160 °C, can be used in the formation of **149** from **150**.

Scheme 43



5

2,3,4,4a,9,9a-Hexahydro-1H-3-aza-fluoren-6-ylamine may be prepared by the method found in Scheme 43.

Nitrobenzylpyridines **151** are alkylated, such as with MeI, in the presence of TBAI and base to form the pyridinium compound **152**. The pyridinium compounds **152** are halogenated, such as brominated with NBS, to form the brominated pyridinium compounds **153** which are reduced such as with NaBH_4 to form the tetrahydro-pyridines **154**. Palladium catalyzed intramolecular Heck coupling followed by hydrogenation forms the hexahydro-fluorenes **156**.

The starting compounds defined in Schemes 1-43 may also be present with functional groups in protected form if necessary and/or in the form of salts, provided a salt-forming group is present and the reaction in salt form is possible. If so desired, one compound of Formula I-IV can be converted into another compound of Formula I-IV or an N-oxide thereof; a compound of Formula I-IV can be converted into a salt; a salt of a compound of Formula I-IV can be converted into the free compound or another salt; and/or a mixture of isomeric compounds of Formula I-IV can be separated into the individual isomers.

N-Oxides can be obtained in a known manner by reacting a compound of Formula I-IV with hydrogen peroxide or a peracid, e.g., 3-chloroperoxy-benzoic acid, in an inert solvent, e.g., CH_2Cl_2 , at a temperature between about -10-35 °C, such as about 0 °C - RT.

If one or more other functional groups, for example carboxy, hydroxy, amino, or mercapto, are or need to be protected in a compound of Formula I-IV or in the synthesis of a compound of Formula I-IV, because they should not take part in the reaction, these are such groups as are usually used in the synthesis of peptide compounds, and also of cephalosporins and penicillins, as well as nucleic acid derivatives and sugars.

The protecting groups may already be present in precursors and should protect the functional groups concerned against unwanted secondary reactions, such as acylations, etherifications, esterifications, oxidations, solvolysis, and similar reactions. It is a characteristic of protecting groups that they lend themselves readily, i.e. without undesired secondary reactions, to removal, typically by solvolysis, reduction, photolysis or also by enzyme activity, for example under conditions analogous to physiological conditions, and that they are not present in

the end-products. The specialist knows, or can easily establish, which protecting groups are suitable with the reactions mentioned above and hereinafter.

5 The protection of such functional groups by such protecting groups, the protecting groups themselves, and their removal reactions are described for example in standard reference works, such as J.F.W. McOmie, *Protective Groups in Organic Chemistry*, Plenum Press, London and New York (1973), in T.W. Greene, *Protective Groups in Organic*
10 *Synthesis*, Wiley, New York (1981), in *The Peptides*, Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York (1981), in *Methoden der Organischen Chemie (Methods of Organic Chemistry)*, Houben Weyl, 4th edition, Volume 15/1, Georg Thieme Verlag, Stuttgart (1974),
15 in H.-D. Jakubke and H. Jescheit, *Aminosäuren, Peptide, Proteine (Amino Acids, Peptides, Proteins)*, Verlag Chemie, Weinheim, Deerfield Beach, and Basel (1982), and in Jochen Lehmann, *Chemie der Kohlenhydrate: Monosaccharide und Derivate (Chemistry of Carbohydrates: Monosaccharides and*
20 *Derivatives)*, Georg Thieme Verlag, Stuttgart (1974).

In the additional process steps, carried out as desired, functional groups of the starting compounds which should not take part in the reaction may be present in unprotected form or may be protected for example by one or
25 more of the protecting groups mentioned above under "protecting groups". The protecting groups are then wholly or partly removed according to one of the methods described there.

Salts of a compound of Formula I-IV with a salt-forming group may be prepared in a manner known *per se*. Acid
30 addition salts of compounds of Formula I-IV may thus be obtained by treatment with an acid or with a suitable anion exchange reagent. A salt with two acid molecules (for example a dihalogenide of a compound of Formula I) may also

be converted into a salt with one acid molecule per compound (for example a monohalogenide); this may be done by heating to a melt, or for example by heating as a solid under a high vacuum at elevated temperature, for example from about 130
5 °C to about 170 °C, one molecule of the acid being expelled per molecule of a compound of Formula I-IV.

Salts can usually be converted to free compounds, e.g., by treating with suitable basic agents, for example with alkali metal carbonates, alkali metal hydrogen
10 carbonates, or alkali metal hydroxides, typically potassium carbonate or sodium hydroxide.

A compound of Formula I, wherein Z is oxygen, can be converted into the respective compound wherein Z is sulfur, for example, by using an appropriate sulfur compound, e. g.
15 using reaction with Lawesson's reagent (2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide) in a halogenated hydrocarbon, such as CH_2Cl_2 , or an aprotic solvent, such as toluene or xylene, at temperatures from about 30 °C to reflux.

20 All process steps described here can be carried out under known reaction conditions, preferably under those specifically mentioned, in the absence of or usually in the presence of solvents or diluents, preferably such as are inert to the reagents used and able to dissolve these, in
25 the absence or presence of catalysts, condensing agents or neutralizing agents, for example ion exchangers, typically cation exchangers, for example in the H^+ form, depending on the type of reaction and/or reactants at reduced, normal, or elevated temperature, for example in the range from about
30 -100 °C to about 190 °C, preferably from about -80 °C to about 150 °C, for example at about -80 to about 60 °C, at RT, at about -20 °C to about 40 °C or at the boiling point of the solvent used, under atmospheric pressure or in a

closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under argon or nitrogen.

Salts may be present in all starting compounds and transients, if these contain salt-forming groups. Salts may
5 also be present during the reaction of such compounds, provided the reaction is not thereby disturbed.

In certain cases, typically in hydrogenation processes, it is possible to achieve stereoselective reactions, allowing for example easier recovery of
10 individual isomers.

The solvents from which those can be selected which are suitable for the reaction in question include for example water, esters, typically lower alkyl-lower alkanooates, e.g., ethyl acetate, ethers, typically aliphatic
15 ethers, e.g., diethyl ether, or cyclic ethers, e.g., THF, liquid aromatic hydrocarbons, typically benzene or toluene, alcohols, typically MeOH, EtOH or 1-propanol, IpOH, nitriles, typically CH_3CN , halogenated hydrocarbons, typically CH_2Cl_2 , acid amides, typically DMF, bases,
20 typically heterocyclic nitrogen bases, e.g. pyridine, carboxylic acids, typically lower alkanecarboxylic acids, e.g., AcOH, carboxylic acid anhydrides, typically lower alkane acid anhydrides, e.g., acetic anhydride, cyclic, linear, or branched hydrocarbons, typically cyclohexane,
25 hexane, or isopentane, or mixtures of these solvents, e.g., aqueous solutions, unless otherwise stated in the description of the process. Such solvent mixtures may also be used in processing, for example in chromatography.

The invention relates also to those forms of the
30 process in which one starts from a compound obtainable at any stage as a transient and carries out the missing steps, or breaks off the process at any stage, or forms a starting material under the reaction conditions, or uses said starting material in the form of a reactive derivative or

salt, or produces a compound obtainable by means of the process according to the invention and processes the said compound *in situ*. In the preferred embodiment, one starts from those starting materials which lead to the compounds described above as preferred.

The compounds of Formula I-IV, including their salts, are also obtainable in the form of hydrates, or their crystals can include for example the solvent used for crystallization (present as solvates).

New starting materials and/or intermediates, as well as processes for the preparation thereof, are likewise the subject of this invention. In the preferred embodiment, such starting materials are used and reaction conditions so selected as to enable the preferred compounds to be obtained.

Starting materials of the invention, are known, are commercially available, or can be synthesized in analogy to or according to methods that are known in the art.

For example, amine **1** can be prepared by reduction of the corresponding nitro. The reduction preferably takes place in the presence of a suitable reducing agent, such as tin(II) chloride or hydrogen in the presence of an appropriate catalyst, such as Raney nickel (then preferably the hydrogen is used under pressure, e.g. between 2 and 20 bar) or PtO₂, in an appropriate solvent, e.g. an alcohol, such as MeOH. The reaction temperature is preferably between about 0 °C and about 80 °C, especially about 15 °C to about 30 °C.

It would also be possible to reduce the nitro compound after forming the amide compound under reaction conditions analogous to those for the reduction of nitro compounds described above. This would eliminate the need to protect the free amino group as described in Scheme 1.

In the preparation of starting materials, existing functional groups which do not participate in the reaction should, if necessary, be protected. Preferred protecting groups, their introduction and their removal are described
5 above or in the examples.

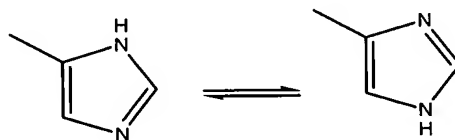
All remaining starting materials are known, capable of being prepared according to known processes, or commercially obtainable; in particular, they can be prepared using processes as described in the examples.

10 Compounds of the present invention can possess, in general, one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or non-racemic mixtures thereof. The optical isomers can be obtained by resolution of the
15 racemic mixtures according to conventional processes, e.g., by formation of diastereoisomeric salts, by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric, and camphorsulfonic acid and then
20 separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the
25 separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of the invention with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be
30 separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of the invention can likewise be obtained by using optically active starting

materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

The compounds of this invention may contain one or more asymmetric centers and thus occur as racemates and
5 racemic mixtures, scalemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of these compounds are expressly included in the present invention.

The compounds of this invention may also be
10 represented in multiple tautomeric forms, for example, as illustrated below:



15 The invention expressly includes all tautomeric forms of the compounds described herein.

The compounds may also occur in cis- or trans- or E- or Z- double bond isomeric forms. All such isomeric forms of such compounds are expressly included in the present
20 invention. All crystal forms of the compounds described herein are expressly included in the present invention.

Substituents on ring moieties (e.g., phenyl, thienyl, etc.) may be attached to specific atoms, whereby they are intended to be fixed to that atom, or they may be drawn
25 unattached to a specific atom, whereby they are intended to be attached at any available atom that is not already substituted by an atom other than H (hydrogen).

The compounds of this invention may contain heterocyclic ring systems attached to another ring system.
30 Such heterocyclic ring systems may be attached through a carbon atom or a heteroatom in the ring system.

Alternatively, a compound of any of the formulas delineated herein may be synthesized according to any of the processes delineated herein. In the processes delineated herein, the steps may be performed in an alternate order and
5 may be preceded, or followed, by additional protection/deprotection steps as necessary. The processes may further comprise use of appropriate reaction conditions, including inert solvents, additional reagents, such as bases (e.g., LDA, DIEA, pyridine, K_2CO_3 , and the like), catalysts,
10 and salt forms of the above. The intermediates may be isolated or carried on *in situ*, with or without purification. Purification methods are known in the art and include, for example, crystallization, chromatography (liquid and gas phase, simulated moving bed ("SMB")),
15 extraction, distillation, trituration, reverse phase HPLC and the like. Reaction conditions such as temperature, duration, pressure, and atmosphere (inert gas, ambient) are known in the art and may be adjusted as appropriate for the reaction.

20 As can be appreciated by the skilled artisan, the above synthetic schemes are not intended to comprise a comprehensive list of all means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of
25 ordinary skill in the art. Additionally, the various synthetic steps described above may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in
30 synthesizing the inhibitor compounds described herein are known in the art and include, for example, those such as described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd

edition, John Wiley and Sons (1999); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); A. Katritzky and A. Pozharski, *Handbook of Heterocyclic Chemistry*, 2nd edition (2001); M.
5 Bodanszky, A. Bodanszky: *The Practice of Peptide Synthesis* Springer-Verlag, Berlin Heidelberg (1984); J. Seyden-Penne: *Reductions by the Alumino- and Borohydrides in Organic Synthesis*, 2nd edition, Wiley-VCH (1997); and L. Paquette, editors, *Encyclopedia of Reagents for Organic Synthesis*,
10 John Wiley and Sons (1995).

The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration
15 into a given biological compartment (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The following examples contain detailed descriptions
20 of the methods of preparation of compounds of Formulas I-IV. These detailed descriptions fall within the scope, and serve to exemplify, the above-described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only
25 and are not intended as a restriction on the scope of the invention.

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents such as DMF, THF, CH₂Cl₂
30 and toluene were obtained from the Aldrich Chemical Company. All reactions involving air- or moisture-sensitive compounds were performed under a nitrogen atmosphere. Flash chromatography was performed using Aldrich Chemical Company silica gel (200-400 mesh, 60A) or Biotage pre-packed column.

Thin-layer chromatography (TLC) was performed with Analtech gel TLC plates (250 μ). Preparative TLC was performed with Analtech silica gel plates (1000-2000 μ). Preparative HPLC was conducted on Beckman or Waters HPLC system with 0.1% TFA/H₂O and 0.1% TFA/CH₃CN as mobile phase. The flow rate was at 20 mL/min. and gradient method was used. ¹H NMR spectra were determined with super conducting FT NMR spectrometers operating at 400 MHz or a Varian 300 MHz instrument. Chemical shifts are expressed in ppm downfield from internal standard tetramethylsilane. All compounds showed NMR spectra consistent with their assigned structures. Mass spectra (MS) were determined on a Perkin Elmer - SCIEX API 165 electrospray mass spectrometer (positive and, or negative) or an HP 1100 MSD LC-MS with electrospray ionization and quadrupole detection. All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated.

The following abbreviations are used:

20

AcOH -	acetic acid
Ac ₂ O -	acetic anhydride
AIBN -	2,2'-azobisisobutyronitrile
Ar -	argon
25 AgSO ₄ -	silver sulfate
AlCl ₃ -	aluminum trichloride
ATP -	adenosine triphosphate
BH ₃ -	borane
Boc -	tert-butyloxycarbonyl
30 Boc ₂ O -	Boc anhydride
BOP-Cl -	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
Br ₂ -	bromine

	BSA -	bovine serum albumin
	t-BuOH -	tert-butanol
	CAN -	ammonium cerium(IV) nitrate
	CH ₃ CN, AcCN -	acetonitrile
5	CH ₂ Cl ₂ -	dichloromethane
	CH ₃ I, MeI -	iodomethane, methyl iodide
	CCl ₄ -	carbon tetrachloride
	CCl ₃ -	chloroform
	CO ₂ -	carbon dioxide
10	Cs ₂ CO ₃ -	cesium carbonate
	DIEA -	diisopropylethylamine
	CuI -	copper iodide
	CuCN -	copper cyanide
	DCE -	1,2-dichloroethane
15	DEAD -	diethyl azodicarboxylate
	DIEA -	diisopropylethylamine
	dppf -	1,1-diphenylphosphinoferrocene
	DMAP -	4-(dimethylamino)pyridine
	DMAC -	N,N-dimethylacetamide
20	DMF -	dimethylformamide
	DMSO -	dimethylsulfoxide
	DTT -	dithiothreitol
	EDC, EDAC-	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
25	EGTA -	ethylene glycol-bis(β-aminoethyl ether)-N,N,N',N'-tetraacetic acid
	EtOAc -	ethyl acetate
	EtOH -	ethanol
	Et ₂ O -	diethyl ether
30	Fe -	iron
	g -	gram
	h -	hour
	HATU -	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

	H ₂ -	hydrogen
	H ₂ O -	water
	HCl -	hydrochloric acid
	H ₂ SO ₄ -	sulfuric acid
5	H ₂ NNH ₂ -	hydrazine
	HC(OEt) ₃ -	triethylorthoformate
	HCHO, H ₂ CO -	formaldehyde
	HCO ₂ Na -	sodium formate
	HOAc, AcOH -	acetic acid
10	HOAt -	1-hydroxy-7-azabenzotriazole
	HOBT -	hydroxybenzotriazole
	IpOH -	isopropanol
	KF -	potassium fluoride
	K ₂ CO ₃ -	potassium carbonate
15	KHMDS -	potassium hexamethylsilazane
	KNO ₃ -	potassium nitrate
	KOAc -	potassium acetate
	KOH -	potassium hydroxide
	LAH, LiAlH ₄ -	lithium aluminum hydride
20	LDA -	lithium diisopropylamide
	LiCl -	lithium chloride
	LiHMDS -	lithium hexamethyldisilazide
	MeOH -	methanol
	MgCl ₂ -	magnesium chloride
25	MgSO ₄ -	magnesium sulfate
	mg -	milligram
	mL -	milliliter
	MnCl ₂ -	manganese chloride
	NBS -	N-bromosuccinimide
30	NMO -	4-methylmorpholine, N-oxide
	NMP -	N-methylpyrrolidone
	Na ₂ SO ₄ -	sodium sulfate
	Na ₂ S ₂ O ₅ -	sodium metabisulfite
	NaHSO ₃ -	sodium bisulfite

	NaHCO_3 -	sodium bicarbonate
	Na_2CO_3 -	sodium carbonate
	NaCl -	sodium chloride
	NaH -	sodium hydride
5	NaI -	sodium iodide
	NaOH -	sodium hydroxide
	NaOMe -	sodium methoxide
	NaOEt -	sodium ethoxide
	NaCNBH_3 -	sodium cyanoborohydride
10	NaBH_4 -	sodium borohydride
	NaNO_2 -	sodium nitrate
	$\text{NaBH}(\text{OAc})_3$ -	sodium triacetoxymethylborohydride
	NH_4Cl -	ammonium chloride
	N_2 -	nitrogen
15	Pd/C -	palladium on carbon
	$\text{PdCl}_2(\text{PPh}_3)_2$ -	palladium chloride bis(triphenylphosphine)
	$\text{PdCl}_2(\text{dppf})$ -	1,1-bis(diphenylphosphino)ferrocene palladium chloride
	$\text{Pd}(\text{PPh}_3)_4$ -	palladium tetrakis triphenylphosphine
20	$\text{Pd}(\text{OH})_2$ -	palladium hydroxide
	$\text{Pd}(\text{OAc})_2$ -	palladium acetate
	PMB -	para methoxybenzyl
	POCl_3 -	phosphorus oxychloride
	PPh_3 -	triphenylphosphine
25	PtO_2 -	platinum oxide
	RT -	room temperature
	SiO_2 -	silica
	SOCl_2 -	thionyl chloride
	TBAI -	tetrabutylammonium iodide
30	TBTU -	O-(1H-benzotriazol-1-yl)-N,N,N',N'- tetramethyluronium tetrafluoroborate
	TEA -	triethylamine
	Tf_2NPh -	N-phenyltrifluoromethanesulfonimide
	TFA -	trifluoroacetic acid

THF - tetrahydrofuran
TPAP - tetrapropylammoniumperruthenate
Tris-HCl - Tris(hydroxymethyl)aminomethane
hydrochloride salt
5 Zn - zinc

Preparation I - 3-nitro-5-trifluoromethyl-phenol:

1-Methoxy-3-nitro-5-trifluoromethyl-benzene (10g, Aldrich)
and pyridine-HCl (41.8g, Aldrich) were mixed together and
10 heated neat at 210 °C in an open flask. After 2.5 h the
mixture was cooled to RT and partitioned between 1N HCl and
EtOAc. The EtOAc fraction was washed with 1 N HCl (4x),
brine (1x), dried with Na₂SO₄, filtered and concentrated in
vacuo to form 3-nitro-5-trifluoromethyl-phenol as an off-
15 white solid.

**Preparation II - 1-Boc-4-(3-nitro-5-trifluoromethyl-
phenoxy)-piperidine:**

3-Nitro-5-trifluoromethyl-phenol (8.81 g) was dissolved in
20 THF (76 mL). 1-Boc-4-hydroxy-piperidine (8.81 g, Aldrich)
and Ph₃P (11.15 g) were added and the solution was cooled to
-20 °C. A solution of DEAD (6.8 mL, Aldrich) in THF (36 mL)
was added dropwise, maintaining the temperature between -20
and -10 °C. The reaction was warmed to RT and stirred
25 overnight. The reaction was concentrated in vacuo and
trituated with hexane. The yellow solid was removed by
filtration and washed with Et₂O (25 mL), and hexane. The
white filtrate was washed with 1 N NaOH (2x), brine (1x) and
the hexane layer was dried over Na₂SO₄, filtered and
30 concentrated in vacuo. The crude material was purified with
flash chromatography (SiO₂, 5-10% EtOAc/hexane) to obtain 1-
Boc-4-(3-nitro-5-trifluoromethyl-phenoxy)-piperidine.

The following compounds were prepared similarly to the procedure outlined above:

- 5 a) (S)-1-Boc-[2-(5-nitro-2-trifluoromethylphenoxy)methyl]-pyrrolidine
- b) (R)-1-Boc-[2-(5-nitro-2-trifluoromethylphenoxy)methyl]-pyrrolidine.
- c) (R) 1-Boc-2-(3-Nitro-5-trifluoromethyl-phenoxy)methyl)-pyrrolidine
- 10 d) 4-(2-tert-Butyl-5-nitro-phenoxy)methyl)-1-methyl-piperidine.
- e) (S) 1-Boc-2-(3-Nitro-5-trifluoromethyl-phenoxy)methyl)-pyrrolidine
- f) 1-Boc-3-(5-nitro-2-pentafluoroethyl-phenoxy)methyl)-azetidine.
- 15 g) N-Boc-[2-(5-nitro-2-pentafluoroethyl-phenoxy)-ethyl]amine.
- h) (R) 3-(2-tert-Butyl-5-nitro-phenoxy)methyl)-1-Boc-pyrrolidine.
- 20 i) 3-(2-tert-Butyl-5-nitro-phenoxy)methyl)-1-Boc-azetidine.
- j) (S)-1-Boc-[2-(5-nitro-2-tert-butylphenoxy)methyl]-pyrrolidine
- k) (S) 3-(2-tert-Butyl-5-nitro-phenoxy)methyl)-1-Boc-pyrrolidine.
- 25 l) (R)-1-Boc-[2-(5-nitro-2-tert-butylphenoxy)methyl]-pyrrolidine

Preparation III - 1-Boc-4-(3-amino-5-trifluoromethyl-phenoxy)-piperidine:

- 30 1-Boc-4-(3-nitro-5-trifluoromethyl-phenoxy)-piperidine (470 mg) was dissolved in MeOH (12 mL) and Pd/C (10 mg) was added. After sparging briefly with H₂, the mixture was stirred under H₂ for 6 H. The catalyst was removed by filtration and the MeOH solution was concentrated in

vacuo to yield 1-Boc-4-(3-amino-5-trifluoromethyl-phenoxy)-piperidine as an off-white foam.

5 The following compounds were prepared similarly to the procedure outlined above:

- a) 1-Boc-2-(3-Amino-5-trifluoromethyl-phenoxy)methyl)-pyrrolidine.
- b) 2-(3-Amino-5-trifluoromethyl-phenoxy)methyl)-1-methyl-pyrrolidine.
- 10 c) [2-(1-Methylpiperidin-4-yloxy)-pyridin-4-yl]methylaniline. ESI (M+H)=222.
- d) [2-(2-Morpholin-4-yl-ethoxy)-pyridin-4-yl]methylaniline.
- e) [2-(2-Morpholin-4-yl-propoxy)-pyridin-4-yl]methylaniline.
- 15 f) [2-(1-Methyl-pyrrolidin-2-ylmethoxy)-pyridin-4-yl]methylaniline. ESI MS: (M+H)=222.
- g) (4-Aminomethyl-pyridin-2-yl)-(3-morpholin-4-yl-propyl)-amine. ESI MS: (M+H)=251.
- h) 4-tert-Butyl-3-(1-methyl-piperidin-4-ylmethoxy)-phenylaniline.
- 20 i) 4-tert-Butyl-3-(2-piperidin-1-yl-ethoxy)-phenylaniline.
- j) 3-(1-Methyl-piperidin-4-ylmethoxy)-4-pentafluoroethyl-phenylaniline.
- k) 3-(1-Isopropyl-piperidin-4-ylmethoxy)-4-pentafluoroethyl-phenylaniline.
- 25 l) (S) 3-Oxiranylmethoxy-4-pentafluoroethyl-phenylaniline.
- m) 3-(2-Pyrrolidin-1-yl-ethoxy)-4-trifluoromethyl-phenylaniline.
- n) 3-(2-Piperidin-1-yl-ethoxy)-4-trifluoromethyl-phenylaniline.
- 30 o) (S) 3-(1-Boc-pyrrolidin-2-ylmethoxy)-4-pentafluoroethyl-phenylaniline.
- p) (R) 3-(1-Boc-pyrrolidin-2-ylmethoxy)-4-pentafluoroethyl-phenylaniline.

- q) (R) 3-(1-Methyl-pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenylamine.
- r) (S) 3-(1-Methyl-pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenylamine
- 5 s) (R) 3-Oxiranylmethoxy-4-pentafluoroethyl-phenylamine.
- t) (R) 2-(5-Amino-2-pentafluoroethyl-phenoxy)-1-pyrrolidin-1-yl-ethanol.
- u) 3-(1-Boc-azetidin-3-ylmethoxy)-4-pentafluoroethyl-phenylamine.
- 10 v) 3-(2-(Boc-amino)ethoxy)-4-pentafluoroethyl-phenylamine.
- w) 6-Amino-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one. M+H 193.2. Calc'd 192.1.
- x) 2,2,4-Trimethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylamine.
- 15 y) 1-(6-Amino-2,2-dimethyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-ethanone. M+H 221.4. Calc'd 220.3.
- z) [2-(1-Benzhydryl-azetidin-3-yloxy)-pyridin-4-yl]-methylamine.
- aa) [2-(1-Methyl-piperidin-4-ylmethoxy)-pyridin-4-yl]-methylamine. M+H 236.3. Calc'd 235.2.
- 20 ab) 3-(4-Boc-piperazin-1-ylmethyl)-5-trifluoromethyl-phenylamine. M+H 360.3.
- ac) 2-Boc-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-ylamine.
- 25 ad) 3-Morpholin-4-ylmethyl-4-pentafluoroethyl-phenylamine.
- ae) 3-(4-Methyl-piperazin-1-ylmethyl)-4-pentafluoroethyl-phenylamine. M+H 410.3. Calc'd 409.4.
- af) 7-Amino-2-(4-methoxy-benzyl)-4,4-dimethyl-3,4-dihydro-2H-isoquinolin-1-one. M+H 311.1.
- 30 ag) 7-Amino-4,4-dimethyl-3,4-dihydro-2H-isoquinolin-1-one.
- ah) (3-Amino-5-trifluoromethyl-phenyl)-(4-Boc-piperazin-1-yl)-methanone. M+H 374.3; Calc'd 373.
- ai) 3-(4-Boc-Piperazin-1-ylmethyl)-5-trifluoromethyl-phenylamine.

- aj) 1-(7-Amino-4,4-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone. M+H 219.2.
- ak) {2-[2-(1-Methylpiperidin-4-yl)ethoxy]-pyridin-4-yl}-methylamine.
- 5 al) {2-[2-(1-Pyrrolidinyl)ethoxy]-pyridin-4-yl}-methylamine.
- am) {2-[2-(1-Methylpyrrolin-2-yl)ethoxy]-pyridin-4-yl}-methylamine.
- an) (2-Chloro-pyrimidin-4-yl)-methylamine.
- ao) 3-(1-Boc-azetidin-3-ylmethoxy)-5-trifluoromethyl-phenylamine.
- 10 ap) 4-tert-Butyl-3-(1-Boc-pyrrolidin-3-ylmethoxy)-phenylamine. M+H 385.
- aq) 4-tert-Butyl-3-(1-Boc-azetidin-3-ylmethoxy)-phenylamine. M+Na 357.
- 15 ar) (S) 4-tert-Butyl-3-(1-Boc-pyrrolidin-2-ylmethoxy)-phenylamine. M+Na 371.
- as) 3-tert-Butyl-4-(4-Boc-piperazin-1-yl)-phenylamine
- at) 3-(1-Methyl-piperidin-4-yl)-5-trifluoromethyl-phenylamine.
- 20 au) 3,3-Dimethyl-2,3-dihydro-benzofuran-6-ylamine.
- av) 3,9,9-Trimethyl-2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluoren-6-ylamine.
- aw) 4-[1-Methyl-1-(1-methyl-piperidin-4-yl)-ethyl]-phenylamine was prepared using EtOH as the solvent.
- 25 ax) 4-tert-Butyl-3-(4-pyrrolidin-1-yl-but-1-enyl)-phenylamine.
- ay) (R) 3-(1-Boc-pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenylamine.
- az) (S) 3-(1-Boc-pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenylamine.
- 30

Preparation IV - 1-Boc-4-{3-[(2-fluoro-pyridine-3-carbonyl)-amino]-5-trifluoromethyl-phenoxy}-piperidine:

1-Boc-4-(3-amino-5-trifluoromethyl-phenoxy)-piperidine (4.37 g) was dissolved in CH₂Cl₂ (100 mL) and NaHCO₃ (2.4 g, Baker) was added. 2-Fluoropyridine-3-carbonyl chloride (2.12 g) was added and the reaction was stirred at RT for 2.5 h. The reaction was filtered and concentrated *in vacuo* to yield a yellow foam. (30%) EtOAc/Hexane was added and 1-Boc-4-{3-[(2-fluoro-pyridine-3-carbonyl)-amino]-5-trifluoromethyl-phenoxy}-piperidine precipitated as an off white solid.

The following compounds were prepared similarly to the procedure outlined above:

- 15 a) 2-Fluoro-N-[3-(3-piperidin-1-yl-propyl)-5-trifluoromethyl-phenyl]-nicotinamide.
- b) N-[4-tert-Butyl-3-(2-piperidin-1-yl-ethoxy)-phenyl]-2-fluoro-nicotinamide.
- c) N-[3,3-Dimethyl-1-(1-methyl-piperidin-4-ylmethyl)-2,3-dihydro-1H-indol-6-yl]-2-fluoro-nicotinamide.
- 20 d) N-[1-(2-Dimethylamino-acetyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl]-2-fluoro-nicotinamide
- e) N-[3,3-Dimethyl-1-(2-(Boc-amino)acetyl)-2,3-dihydro-1H-indol-6-yl]-2-fluoro-nicotinamide.
- 25 f) N-(4-Acetyl-2,2-dimethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-2-fluoro-nicotinamide. M+H 344.5. Calc'd 343.4.
- g) 2-Fluoro-N-(2,2,4-trimethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-nicotinamide. M+H 316.2. Calc'd 315.1.
- 30 h) N-(2,2-Dimethyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-2-fluoro-nicotinamide. M+H 316.1. Calc'd 315.10.
- i) 2-Fluoro-N-[3-(4-methyl-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-nicotinamide. M+H 481. Calc'd 480.

- j) 2-Fluoro-N-(2-Boc-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-nicotinamide. M+H 400.
- k) 2-Fluoro-N-[3-(4-methyl-piperazin-1-ylmethyl)-4-pentafluoroethyl-phenyl]-nicotinamide. M+H 447.0.
5 Calc'd 446.
- l) 2-Fluoro-N-(3-morpholin-4-ylmethyl-4-pentafluoroethyl-phenyl)-nicotinamide.
- m) 2-Fluoro-N-[4-iodophenyl]-nicotinamide.
- n) 2-Fluoro-N-(4,4-dimethyl-1-oxo-1,2,3,4-tetrahydro-isoquinolin-7-yl)-nicotinamide. M+H 314.0, Calc'd 311.
10
- o) 2-Fluoro-N-[3-(4-Boc-piperazine-1-carbonyl)-5-trifluoromethyl-phenyl]-nicotinamide. M+H 495.
- p) 2-Fluoro-N-[3-(4-Boc-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-nicotinamide. M+H 483.3; Calc'd
15 482.
- q) N-(2-Acetyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-fluoro-nicotinamide. M+H 430.0.
- r) N-[3,3-Dimethyl-1-(1-methyl-piperidin-4-yl)-2,3-dihydro-1H-indol-6-yl]-2-fluoro-nicotinamide. M+H 383.2; Calc'd
20 382.5.
- s) N-(4-tert-Butylphenyl)-2-fluoronicotinamide.
- t) N-(4-Trifluoromethylphenyl)-2-fluoronicotinamide.
- u) 2-Fluoro-N-[3-(1-Boc-azetidin-3-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide. M-H 468.2; Calc'd
25 469.16.
- v) 2-Fluoro-N-[3-(1-Boc-azetidin-3-ylmethoxy)-4-tert-butyl-phenyl]-nicotinamide.
- w) (S) N-[4-tert-Butyl-3-(1-Boc-pyrrolidin-2-ylmethoxy)-phenyl]-2-fluoro-nicotinamide. M+Na 494.
- 30 x) N-[3-(1-Methyl-piperidin-4-yl)-5-trifluoromethyl-phenyl]-2-fluoro-nicotinamide was prepared with K_2CO_3 . instead of $NaHCO_3$.
- y) N-(3-Bromo-5-trifluoromethyl-phenyl)-2-fluoro-nicotinamide.

- z) 2-Fluoro-N-(3,9,9-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluoren-6-yl)-nicotinamide.
- aa) 2-Fluoro-N-{4-[1-methyl-1-(1-methyl-piperidin-4-yl)-ethyl]-phenyl}-nicotinamide
- 5 ab) N-[3,3-Dimethyl-1-(1-Boc-piperidin-4-ylmethyl)-2,3-dihydro-1H-indol-6-yl]-2-fluoro-nicotinamide.

Preparation V - 1-Boc-4-{3-[(2-chloro-pyridine-3-carbonyl)-amino]-5-trifluoromethyl-phenoxy}-piperidine:

- 10 1-Boc-4-{3-[(2-chloro-pyridine-3-carbonyl)-amino]-5-trifluoromethyl-phenoxy}-piperidine was prepared from 1-Boc-4-(3-amino-5-trifluoromethyl-phenoxy)-piperidine and 2-chloropyridine-3-carbonyl chloride by a procedure similar to that described in the preparation of 1-Boc-4-{3-[(2-fluoro-pyridine-3-carbonyl)-amino]-5-trifluoromethyl-phenoxy}-piperidine.
- 15

The following compounds were prepared similarly to the procedure outlined above:

- 20
- a) N-(4-tert-Butyl-3-nitro-phenyl)-2-chloro-nicotinamide.
- b) 2-Chloro-N-[3-(3-piperidin-1-yl-propyl)-5-trifluoromethyl-phenyl]-nicotinamide.
- c) 2-Chloro-N-[3-(3-morpholin-4-yl-propyl)-5-trifluoromethyl-phenyl]-nicotinamide.
- 25
- d) 2-Chloro-N-[3-(1-methylpiperidin-4-yl)-5-trifluoromethyl-phenyl]-nicotinamide.
- e) 2-Chloro-N-[3-(1-methyl-piperidin-4-ylmethoxy)-4-pentafluoroethyl-phenyl]-nicotinamide.
- 30 f) 2-Chloro-N-[3-(1-isopropyl-piperidin-4-ylmethoxy)-4-pentafluoroethyl-phenyl]-nicotinamide.
- g) (S) 2-Chloro-N-[4-(oxiranylmethoxy)-3-pentafluoroethyl-phenyl]-nicotinamide.

- h) 2-Chloro-N-[3-(2-pyrrolidin-1-yl-ethoxy)-4-trifluoromethyl-phenyl]-nicotinamide.
- i) 2-Chloro-N-[3-(2-piperidin-1-yl-ethoxy)-4-pentafluoroethyl-phenyl]-nicotinamide.
- 5 j) (R) 2-Chloro-N-[3-(1-Boc-pyrrolidin-2-ylmethoxy)-4-pentafluoroethyl-phenyl]-nicotinamide.
- k) (S) 2-Chloro-N-[3-(1-Boc-pyrrolidin-2-ylmethoxy)-4-pentafluoroethyl-phenyl]-nicotinamide.
- 10 l) (R) 2-Chloro-N-[3-(1-methyl-pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide.
- m) (S) 2-Chloro-N-[3-(1-methyl-pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide.
- n) (R) 2-Chloro-N-[4-(oxiranylmethoxy)-3-pentafluoroethyl-phenyl]-nicotinamide.
- 15 o) (R) Acetic acid 2-{5-[(2-chloro-pyridine-3-carbonyl)-amino]-2-pentafluoroethyl-phenoxy}-1-pyrrolidin-1-ylethyl ester.
- p) 2-Chloro-N-[3-(4-methyl-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-nicotinamide.
- 20 q) 2-Chloro-N-[2-(4-methoxy-benzyl)-4,4-dimethyl-1-oxo-1,2,3,4-tetrahydro-isoquinolin-7-yl]-nicotinamide. M+H 450.2. Calc'd 449.
- r) 2-Chloro-N-(4,4-dimethyl-1-oxo-1,2,3,4-tetrahydro-isoquinolin-7-yl)-nicotinamide. M+H 330.1, Calc'd 329.
- 25 s) 2-Chloro-N-[3-(4-Boc-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-nicotinamide.
- t) 2-{3-[(2-Chloro-pyridine-3-carbonyl)-amino]-phenyl}-2-methyl-propionic acid methyl ester. M+H 405
- 30 u) N-{4-tert-Butyl-3-[2-(1-Boc-piperidin-4-yl)-ethyl]-phenyl}-2-chloro-nicotinamide. M+Na 524. Calc'd 501.1.
- v) N-[3,3-Dimethyl-1,1-dioxo-2,3-dihydro-1H-benzo[d]isothiazol-6-yl]-2-chloro-nicotinamide.
- w) N-[1,1,4,4-Tetramethyl-1,2,3,4-tetrahydro-naphth-6-yl]-2-chloro-nicotinamide.

- x) 2-Chloro-N-[3,3-dimethyl-2,3-dihydro-benzofuran-6-yl]-2-chloro-nicotinamide.
- y) 2-Chloro-N-[3-(1-Boc-piperidin-4-yloxy)-5-trifluoromethyl-phenyl]-nicotinamide.
- 5 z) 2-Chloro-N-[3-(1-methyl-piperidin-4-ylmethyl)-5-trifluoromethyl-phenyl]-nicotinamide.
- aa) 2-Chloro-N-[3-(3-piperidin-1-yl-propyl)-5-trifluoromethyl-phenyl]-nicotinamide.
- ab) N-[4-tert-Butyl-3-(4-pyrrolidin-1-yl-but-1-enyl)-phenyl]-2-chloro-nicotinamide.
- 10 ac) (R) 2-Chloro-N-[3-(1-Boc-pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide.
- ad) (S) 2-Chloro-N-[3-(1-Boc-pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide.

15

Preparation VI - 1-Boc-2-{3-[(2-fluoro-pyridine-3-carbonyl)-amino]-5-trifluoromethyl-phenoxy-methyl}-pyrrolidine:

1-Boc-2-{3-[(2-Fluoro-pyridine-3-carbonyl)-amino]-5-trifluoromethyl-phenoxy-methyl}-pyrrolidine was prepared from

20 1-Boc-2-(3-amino-5-trifluoromethyl-phenoxy-methyl)-pyrrolidine by a procedure similar to that described in the preparation of 1-Boc-4-{3-[(2-fluoro-pyridine-3-carbonyl)-amino]-5-trifluoromethyl-phenoxy}-piperidine.

25 **Preparation VII - 2-(3-nitro-5-trifluoromethyl-phenoxy-methyl)-pyrrolidine:**

1-Boc-2-(3-nitro-5-trifluoromethyl-phenoxy-methyl)-pyrrolidine (2.35 g) was dissolved in CH₂Cl₂ (60 mL) and TFA (20 mL) was added. After stirring for 1 h at RT, the

30 mixture was concentrated in vacuo to yield 2-(3-nitro-5-trifluoromethyl-phenoxy-methyl)-pyrrolidine as an oil that solidified upon standing. The material was used as is without further purification.

The following compounds were prepared similarly to the procedure outlined above:

- 5 a) (4-Aminomethyl-pyrimidin-2-yl)-(3-morpholin-4-yl-propyl)-amine.
b) (4-Aminomethyl-pyrimidin-2-yl)-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-amine.

10 **Preparation VIII - 1-methyl-2-(3-nitro-5-trifluoromethyl-phenoxyethyl)-pyrrolidine:**

2-(3-Nitro-5-trifluoromethyl-phenoxyethyl)-pyrrolidine (6 mmol) was dissolved in CH₃CN (20 mL) and formaldehyde (2.4 mL, 37% aqueous) was added. NaBH₃CN (607 mg) was added, an exotherm was observed. The pH is monitored every 15 min and
15 adjusted to ~7 with AcOH. After 45 min, the mixture was concentrated in vacuo and the residue is dissolved in EtOAc, washed with 6N NaOH, 1 N NaOH, and 2 N HCl (3x). The acid washings were combined, adjusted to ~ pH 10 with solid Na₂CO₃ and extracted with EtOAc (2x). The EtOAc fractions
20 were combined, dried with Na₂SO₄, and purified with flash chromatography (SiO₂, 95:5:0.5 CH₂Cl₂:MeOH:NH₄OH) to afford 1-methyl-2-(3-nitro-5-trifluoromethyl-phenoxyethyl)-pyrrolidine.

25 The following compounds were prepared similarly to the procedure outlined above:

- a) 2-(1-Methylpiperidin-4-yl)-ethanol.
b) 2-{3-[(2-Fluoro-pyridine-3-carbonyl)-amino]-5-
30 trifluoromethyl-phenoxyethyl}-1-methylpyrrolidine.

Preparation IX - 4-tert-butyl-3-nitro-phenylamine:

A mixture of 1,3-dinitro-4-tert-butylbenzene (10.0 g) in H₂O (56 mL) was heated to reflux. A mixture of Na₂S (21.42 g)

and sulfur (2.85 g) in H₂O (34 mL) was added over 1 h via an addition funnel. The reaction maintained at reflux for 1.5 h then cooled to RT and extracted with EtOAc. The organic extracts were combined and washed with H₂O, brine, dried
5 over MgSO₄ and concentrated in vacuo to afford 4-tert-butyl-3-nitro-phenylamine which was used as is without further purification.

Preparation X - N-(3-bromo-5-trifluoromethyl-phenyl)-acetamide:

3-Bromo-5-(trifluoromethyl)phenylamine (5 g, Alfa-Aesar) was dissolved in AcOH (140 mL) and Ac₂O (5.9 mL, Aldrich) was added. The reaction was stirred at RT overnight. The mixture was added slowly to H₂O (~ 700 mL) forming a white
15 precipitate. The solid was isolated by filtration, washed with H₂O and dried under vacuum to yield N-(3-bromo-5-trifluoromethyl-phenyl)-acetamide.

Preparation XI - N-[3-(3-piperidin-1-yl-propyl)-5-trifluoromethyl-phenyl]-acetamide:

Allylpiperidine (1.96 g, Lancaster) was degassed under vacuum, dissolved in 0.5 M 9-BBN in THF (31.2 mL, Aldrich), and heated to reflux for 1 h, then cooled to RT. PD(dppf)Cl₂/CH₂Cl₂ was added to a degassed mixture of N-(3-
25 bromo-5-trifluoromethyl-phenyl)-acetamide, K₂CO₃ (9.8 g) DMF (32.1 mL and H₂O (3 mL). The allyl piperidine solution was added heated to 60 °C for 3 h. After cooling to RT and reheating at 60 °C for 6 h, the mixture was cooled to RT and poured into H₂O. The mixture was extracted with EtOAc (2x),
30 and the EtOAc portion was washed with 2 N HCl (2x) and brine. The aqueous phases were combined and the pH was adjusted to ~ 11 with NaOH (15%) forming a cloudy suspension. The cloudy suspension was extracted with EtOAc (2x) and the EtOAc portion was dried with Na₂SO₄, filtered

and concentrated in vacuo. The crude material was purified by flash chromatography (SiO₂, 95:5:0.5 CH₂Cl₂:MeOH:NH₄OH) to afford N-[3-(3-piperidin-1-yl-propyl)-5-trifluoromethyl-phenyl]-acetamide as a brown oil that solidified under vacuum.

The following compounds were prepared similarly to the procedure outlined above:

- 10 a) N-(3-Morpholin-4-ylpropyl-5-trifluoromethyl-phenyl)-acetamide from 4-allyl-morpholine.
- b) N-(3-(1-methylpiperidin-4-ylmethyl)-5-trifluoromethyl-phenyl)-acetamide from 1-Methyl-4-methylene-piperidine.

15 **Preparation XII - 3-(3-piperidin-1-yl-propyl)-5-trifluoromethyl-phenylamine:**

N-[3-(3-Piperidin-1-yl-propyl)-5-trifluoromethyl-phenyl]-acetamide (1.33 g) was dissolved in EtOH (40 mL) and 12 N HCl (40 mL) was added. After stirring overnight at 70 °C and RT, the mixture was concentrated in vacuo, affording 3-(3-piperidin-1-yl-propyl)-5-trifluoromethyl-phenylamine as a brown oil.

The following compounds were prepared similarly to the procedure outlined above:

- a) 3,3-Dimethyl-6-nitro-2,3-dihydro-1H-indole. M+H 193.1; Calc'd 192.2.
- b) 3-(1-Methyl-piperidin-4-ylmethyl)-5-trifluoromethyl-phenylamine.
- 30 c) 3-Morpholin-4-ylmethyl-5-trifluoromethyl-phenylamine.

Preparation XIII - 3,3-Dimethyl-6-nitro-1-piperidin-4-ylmethyl-2,3-dihydro-1H-indole:

3,3-Dimethyl-1-(1-Boc-piperidin-4-ylmethyl)-6-nitro-2,3-dihydro-1H-indole was dissolved in HCl/EtOAc and stirred for
5 2 h. The mixture was concentrated in vacuo and partitioned between 1,2-dichloroethane and 1N NaOH. The organic layer was removed, washed with brine, dried (Na₂SO₄) and filtered. The material was used without further purification.

10 **Preparation XIV - N-[3-(3-morpholin-4-yl-propyl)-5-trifluoromethyl-phenyl]-acetamide:**

N-[3-(3-Morpholin-4-yl-propyl)-5-trifluoromethyl-phenyl]-acetamide was prepared from allyl morpholine and N-(3-bromo-5-trifluoromethyl-phenyl)-acetamide similar to that
15 described in the preparation of N-[3-(3-piperidin-1-yl-propyl)-5-trifluoromethyl-phenyl]-acetamide.

Preparation XV - 3-(3-morpholin-4-yl-propyl)-5-trifluoromethyl-phenylamine:

20 3-(3-Morpholin-4-yl-propyl)-5-trifluoromethyl-phenylamine was prepared from N-[3-(3-morpholin-4-yl-propyl)-5-trifluoromethyl-phenyl]-acetamide similar to that described in the preparation of 3-(3-piperidin-1-yl-propyl)-5-trifluoromethyl-phenylamine.

25

Preparation XVI - 1-methyl-4-methylene-piperidine:

Ph₃PCH₃I (50 g, Aldrich) was suspended in Et₂O (20 mL) and butyllithium (77.3 mL, 1.6 M in hexanes, Aldrich) was added dropwise. The reaction was stirred for 2 h at RT then 1-
30 methylpiperidone (12.3 mL, Aldrich) was added slowly. The mixture was stirred at RT overnight. The solid was removed by filtration, the volume was reduced to ~ 400 mL and additional solid was removed by filtration. The Et₂O was washed with H₂O (2x) and 2 N HCl (4x). The pH of the acid

washings was adjusted to ~ 11 with 6 N NaOH, then they were extracted with CH₂Cl₂ (4x). The CH₂Cl₂ washings were dried over Na₂SO₄ and concentrated cold *in vacuo* to provide 1-methyl-4-methylene-piperidine which was used as is.

5

Preparation XVII - N-[3-(1-methylpiperidin-4-yl)-5-trifluoromethyl-phenyl]-acetamide:

N-[3-(1-Methylpiperidin-4-yl)-5-trifluoromethyl-phenyl]-acetamide was prepared from 1-methyl-4-methylene-piperidine and N-(3-bromo-5-trifluoromethyl-phenyl)-acetamide similar to that described in the preparation of N-[3-(3-piperidin-1-yl-propyl)-5-trifluoromethyl-phenyl]-acetamide.

Preparation XVIII - 3-(1-methylpiperidin-4-yl)-5-trifluoromethyl-phenylamine:

3-(1-Methylpiperidin-4-yl)-5-trifluoromethyl-phenylamine was prepared from N-[3-(1-methylpiperidin-4-yl)-5-trifluoromethyl-phenyl]-acetamide similar to the procedure described in the preparation of 3-(3-piperidin-1-yl-propyl)-5-trifluoromethyl-phenylamine.

Preparation XIX - 2-(1-methylpiperidin-4-yloxy)-4-pyridylcarbonitrile:

4-Hydroxy-1-methylpiperidine (25.4 g) was dissolved in THF (50 mL) in a 100 mL r.b. flask. NaH/mineral oil mixture (9.58 g) was slowly added to the flask and stirred for 20 min. 2-Chloro-4-cyanopyridine was added to the mixture and stirred at RT until completion. Diluted mixture with EtOAc and added H₂O to quench mixture, then transferred contents to a sep. funnel. The organic phase was collected while the aqueous phase was washed two times with EtOAc. The combined organics were dried over Na₂SO₄, filtered, then concentrated *in vacuo*. Then redissolved mixture in CH₂Cl₂, 10% HCl (300 mL) was added and the mixture was transferred to sep.

funnel. The org. was extracted, while EtOAc along with 300 mL 5 N NaOH was added to the sep. funnel. The organic phases were collected, dried over Na_2SO_4 , filtered and concentrated *in vacuo* affording 2-(1-methylpiperidin-4-yloxy)-4-pyridylcarbonitrile as a brown solid. ESI (M+H) = 218.

The following compounds were prepared similarly to the procedure outlined above:

10

a) 2-(1-methylpiperidin-4-ylmethoxy)-4-pyridylcarbonitrile.
M+H 232.1. Calc'd 231.1.

b) 2-(1-Benzhydryl-azetidin-3-yloxy)-4-pyridylcarbonitrile.
M+H 342.2. Calc'd 341.2.

15

c) 2-(1-methylpiperidin-4-ylethoxy)-4-pyridylcarbonitrile.

d) 2-(1-pyrrolidinylethoxy)-4-pyridylcarbonitrile.

e) 2-(1-methylpyrrolin-2-ylethoxy)-4-pyridylcarbonitrile.

f) 2-[2-(1-Boc-azetidin-3-yl)-ethoxy]-4-pyridylcarbonitrile.

20

Preparation XX - [2-(1-methylpiperidin-4-yloxy)-pyridin-4-yl]methylamine bis hydrochloride:

[2-(1-Methylpiperidin-4-yloxy)-pyridin-4-yl]methylamine was diluted with Et_2O (50 mL) and 1M HCl/ Et_2O (47 mL) was added. The vessel was swirled until precipitate formed.

25

Preparation XXI - 2-(2-morpholin-4-yl-ethoxy)-4-pyridylcarbonitrile:

2-(2-Morpholin-4-yl-ethoxy)-4-pyridylcarbonitrile was prepared from 2-chloro-4-cyanopyridine and 2-morpholin-4-yl-ethanol by a procedure similar to that described in the preparation of 2-(1-methylpiperidin-4-yloxy)-4-pyridylcarbonitrile. The HCl salt was prepared similar to that described for [2-(1-methylpiperidin-4-yloxy)-pyridin-4-yl]methylamine bis hydrochloride.

30

Preparation XXII - 2-morpholin-4-yl-propanol:

LAH powder (1.6 g) was added to a flask while under N₂ atmosphere, immediately followed by THF (50 mL). The
5 mixture was chilled to 0 °C, methyl 2-morpholin-4-yl-propionate (5 g) was added dropwise to the reaction mixture and stirred at 0 °C. After 1 h, the mixture was worked up by adding H₂O (44 mL), 2N NaOH (44 mL), then H₂O (44 mL, 3x). After 30 min of stirring, the mixture was filtered
10 through Celite® and the organic portion was concentrated in vacuo providing 2-morpholin-4-yl-propanol as a colorless oil.

The following compounds were prepared similarly to the
15 procedure outlined above:

a) (1-Methyl-piperidin-4-yl)-methanol. M+H 130.2. Calc'd 129.1.

20 **Preparation XXIII - 2-(2-morpholin-4-yl-propoxy)-4-pyridylcarbonitrile:**

2-(2-Morpholin-4-yl-propoxy)-4-pyridylcarbonitrile was prepared from 2-chloro-4-cyanopyridine and 2-morpholin-4-yl-propanol by a procedure similar to that described in the
25 preparation of 2-(1-methylpiperidin-4-yloxy)-4-pyridylcarbonitrile.

Preparation XXIV - 2-(1-Methyl-pyrrolidin-2-ylmethoxy)-4-pyridylcarbonitrile:

30 2-(1-Methyl-pyrrolidin-2-ylmethoxy)-4-pyridylcarbonitrile was prepared from 2-chloro-4-cyanopyridine and 1-methyl-pyrrolidin-2-ylmethanol by a procedure similar to that described in the preparation of 2-(1-methylpiperidin-4-yloxy)-4-pyridylcarbonitrile. ESI MS: (M+H)=218.

Preparation XXV - 2-(3-morpholin-4-yl-propylamino)-4-pyridylcarbonitrile:

To a flask charged with 2-chloro-4-cyanopyridine (2.0 g),
5 was added the aminopropyl morpholine (2.11 mL). The mixture
was heated to 79 °C for 5 h and stirred. After 5 h the
reaction was incomplete. The mixture was then heated at 60
°C overnight. The crude compound was purified on silica gel
(1-5% MeOH/CH₂Cl₂ gradient). ESI MS: (M+H)=247, (M-H)=245.

10

Preparation XXVI - 5-Nitro-2-pentafluoroethylphenol:

Combined 2-methoxy-4-nitro-1-pentafluoroethylbenzene (9.35
g) and pyridine HCl in a round bottom flask and heated at
210 °C for 1 h then cooled to RT. The mixture was diluted
15 with EtOAc and 2N HCl (>500 mL) until all residue dissolved.
The organic layer was removed, washed with 2 N HCl (2x) and
concentrated *in vacuo*. The residue was dissolved in hexanes
and Et₂O, washed with 2 N HCl, then brine. Dried organic
layer over Na₂SO₄, filtered, concentrated *in vacuo* and dried
20 under high vacuum to provide 5-nitro-2-
pentafluoromethylphenol.

Preparation XXVII - 2-tert-Butyl-5-nitro-aniline:

To H₂SO₄ (98%, 389 mL) in a 500 mL 3-neck flask was added 2-
25 tert-butyl aniline (40.6 mL). The reaction was cooled to -
10 °C and KNO₃ in 3.89 g aliquots was added every 6 min for
a total of 10 aliquots. Tried to maintain temperature at -5
°C to -10 °C. After final addition of KNO₃, stirred the
reaction for five min then it was poured onto ice (50 g).
30 The black mix was diluted with H₂O and extracted with EtOAc.
The aqueous layer was basified with solid NaOH slowly then
extracted with EtOAc (2x). The combined organic layers were
washed with 6 N NaOH and then with a mix of 6 N NaOH and
brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*

to obtain crude 2-tert-butyl-5-nitro-aniline as a dark red-black oil which solidified when standing at RT. The crude material was triturated with about 130 mL hexanes. After decanting the hexanes, the material was dried to obtain a
5 dark-red black solid.

Preparation XXVIII - 2-tert-Butyl-5-nitrophenol:

In a 250 mL round bottom flask, 20 mL concentrated H₂SO₄ was added to 2-tert-butyl-5-nitro-aniline (7.15 g) by adding 5
10 mL aliquots of acid and sonicating with occasional heating until all of the starting aniline went into solution. H₂O (84 mL) was added with stirring, then the reaction was cooled to 0°C forming a yellow-orange suspension. A solution of NaNO₂ (2.792 g) in H₂O (11.2 mL) was added
15 dropwise to the suspension and stirred for 5 min. Excess NaNO₂ was neutralized with urea, then the cloudy solution was transferred to 500 mL 3-necked round bottom flask then added 17 mL of 1:2 H₂SO₄:H₂O solution, and heated at reflux. Two additional 5 mL aliquots of 1:2 H₂SO₄:H₂O solution, a 7
20 mL aliquot of 1:2 H₂SO₄:H₂O solution and another 10 mL of 1:2 H₂SO₄: H₂O were added while heating at reflux. The mixture was cooled to RT forming a black layer floating on top of the aqueous layer. The black layer was diluted with EtOAc (300 mL) and separated. The organic layer was washed with
25 H₂O then brine, dried over Na₂SO₄ and concentrated *in vacuo*. Crude oil was purified on silica gel column with 8% EtOAc/Hexanes. Upon drying under vacuum, the 2-tert-butyl-5-nitrophenol was isolated as a brown solid.

30 **Preparation XXIX - 1-methylpiperidine-4-carboxylic acid ethyl ester:**

Piperidine-4-carboxylic acid ethyl ester (78 g) was dissolved in MeOH (1.2 L) at RT then formaldehyde (37%, 90 mL) and acetic acid (42 mL) were added and stirred for 2 h.

The mixture was cooled to 0 °C, NaCNBH₃ (70 g) was added, and the mix was stirred for 20 min at 0 °C, then overnight at RT. The mixture was cooled to 0 °C then quenched with 6N NaOH. The mixture was concentrated *in vacuo* to an aqueous layer, which was extracted with EtOAc (4x), brine-washed, dried over Na₂SO₄, and concentrated *in vacuo* to provide 1-methylpiperidine-4-carboxylic acid ethyl ester.

The following compounds were prepared similarly to the procedure outlined above:

a) (1-Methyl-piperidin-4-yl)-methanol. M+H 130.2. Calc'd 129.1.

Preparation XXX - N-[4-tert-Butyl-3-(1-methyl-piperidin-4-ylmethoxy)-phenyl]-2-chloro-nicotinamide:

N-[4-tert-Butyl-3-(1-methyl-piperidin-4-ylmethoxy)-phenyl]-2-chloro-nicotinamide was prepared from 4-tert-butyl-3-(1-methyl-piperidin-4-ylmethoxy)-phenylamine by a procedure similar to that described in the preparation of 1-Boc-4-{3-[(2-chloro-pyridine-3-carbonyl)-amino]-5-trifluoromethyl-phenoxy}-piperidine.

Preparation XXXI - 1-[2-(2-tert-Butyl-5-nitro-phenoxy)-ethyl]-piperidine:

To 2-tert-butyl-5-nitrophenol (1.01 g) and K₂CO₃ (1.72 g) was added acetone (35 mL) and H₂O (10.5 mL), then 1-(2-chloroethyl)piperidine HCl (1.909 g) and TBAI (153 mg). The mixture was stirred at reflux overnight. Additional K₂CO₃ (850 mg) and 1-(2-chloroethyl)-piperidine HCl (950 mg) were added and the mixture was heated at reflux for 6 h. The mixture was concentrated *in vacuo* to an aqueous layer which was acidified with 2 N HCl and extracted with EtOAc. The aqueous layer was basified with 6N NaOH and washed with

CH₂Cl₂ (3x). The combined organic layers were washed with brine/1N NaOH and dried over Na₂SO₄. Washed the EtOAc layer with 2N NaOH/brine and dried over Na₂SO₄. The crude material was purified by silica gel column chromatography with 15% EtOAc/Hexanes to yield 1-[2-(2-tert-butyl-5-nitro-phenoxy)-ethyl]-piperidine as a light tan solid.
(M+1)=307.3.

Preparation XXXII - 1-Boc-Piperidine-4-carboxylic acid ethyl ester:

To a stirred solution of piperidine-4-carboxylic acid ethyl ester (23.5 g) in EtOAc (118 mL) at 0 °C was added dropwise Boc₂O in EtOAc (60 mL). The reaction was warmed to RT and stirred overnight. Washed reaction with H₂O, 0.1 N HCl, H₂O, NaHCO₃ and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The liquid was dried under vacuum to provide 1-Boc-piperidine-4-carboxylic acid ethyl ester.

The following compounds were prepared similarly to the procedure outlined above:

- a) N-Boc-(2-chloropyrimidin-4-yl)-methylaniline.
- b) 1-(2-tert-Butyl-4-nitrophenyl)-4-Boc-piperazine.
- c) 1-Boc-azetidine-3-carboxylic acid
- d) 1-Boc-4-Hydroxymethyl-piperidine using TEA.

Preparation XXXIII - 1-Boc-4-hydroxymethyl-piperidine

1-Boc-4-Hydroxymethyl-piperidine was prepared from 1-Boc-piperidine-4-carboxylic acid ethyl ester by a procedure similar to that described in the preparation of 2-morpholin-4-yl-propanol.

Preparation XXXIV - 1-Boc-4-Methylsulfonyloxymethyl-piperidine:

Dissolved 1-Boc-4-hydroxymethyl-piperidine in anhydrous CH_2Cl_2 (50 mL) and TEA (4.5 mL) and cooled to 0 °C. Mesyl chloride (840 μl) was added and the mixture was stirred for 15 min then at RT for 45 min. The mixture was washed with brine/1 N HCl and then brine, dried over Na_2SO_4 , concentrated *in vacuo* and dried under high vacuum to provide 1-Boc-4-methylsulfonyloxymethyl-piperidine as a yellow orange thick oil.

The following compounds were prepared similarly to the procedure outlined above:

a) 1-Boc-3-methylsulfonyloxymethyl-azetidine.

Preparation XXXV - 1-Boc-4-(3-nitro-6-pentafluoroethyl-phenoxyethyl)-piperidine:

To a slurry of 60% NaH suspension in DMF (30 mL) at RT added a solution of 5-nitro-2-pentafluoroethyl-phenol (3.6 g) in 5 mL DMF. The dark red mixture was stirred at RT for 10 min then added a solution of 1-Boc-4-methylsulfonyloxymethyl-piperidine (3.1 g) in 5 mL DMF. The reaction was stirred at 60 °C and 95 °C. After 1h, added 2.94 g K_2CO_3 and stirred overnight at 105 °C. After cooling to RT, the reaction was diluted with hexanes and 1 N NaOH. Separated layers, and washed organic layer with 1 N NaOH and with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification with silica gel column chromatography with 8% EtOAc/Hexanes yielded 1-Boc-4-(3-nitro-6-pentafluoroethyl-phenoxyethyl)-piperidine as a light yellow thick oil.

Preparation XXXVI - 4-(3-nitro-6-pentafluoroethyl-phenoxymethyl)-piperidine:

4-(3-Nitro-6-pentafluoroethyl-phenoxymethyl)-piperidine was prepared from 1-Boc-4-(3-nitro-6-pentafluoroethyl-phenoxymethyl)-piperidine by a procedure similar to that described in the preparation of 2-(3-nitro-5-trifluoromethyl-phenoxymethyl)-pyrrolidine.

Preparation XXXVII - 1-methyl-4-(3-nitro-6-pentafluoroethyl-phenoxymethyl)-piperidine:

4-(3-Nitro-6-pentafluoroethyl-phenoxymethyl)-piperidine (316.5 mg) was dissolved in 2.7 mL CH₃CN, then added 37% formaldehyde/H₂O (360 µL) and then NaBH₃CN (90 mg). Upon addition of NaCNBH₃ the reaction exothermed slightly. The reaction was stirred at RT and pH was maintained at ~7 by addition of drops of glacial AcOH. After about 1 h, the mixture was concentrated *in vacuo*, treated with 8 mL 2 N KOH and extracted two times with 10 mL Et₂O. The organic layers were washed with 0.5 N KOH and then the combined organic layers were extracted two times with 1 N HCl. The aqueous layer was basified with solid KOH and extracted two times with Et₂O. This organic layer was then washed with brine/1N NaOH, dried over Na₂SO₄, filtered, concentrated *in vacuo* and dried under high vacuum to give pure compound.

Preparation XXXVIII - 1-Isopropyl-4-(5-nitro-2-pentafluoroethyl-phenoxymethyl)-piperidine:

Dissolved 4-(5-nitro-2-pentafluoroethyl-phenoxymethyl)-piperidine (646 mg) in 1,2-dichloroethane (6.4 mL), then added acetone (136 µL), NaBH(OAc)₃ (541 mg) and finally AcOH (105 µL). Stirred the cloudy yellow solution under N₂ at RT overnight. Added another 130 µL acetone and stirred at RT over weekend. Quenched the reaction with 30 mL N NaOH/H₂O and stirred 10 min. Extracted with Et₂O and the organic

layer was brine-washed, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Dried under high vacuum for several h to obtain 1-isopropyl-4-(5-nitro-2-pentafluoroethyl-phenoxy-methyl)-piperidine as a yellow orange solid.

5

The following compounds were prepared similarly to the procedure outlined above:

- 10 a) 3,3-Dimethyl-1-(1-methyl-piperidin-4-yl)-6-nitro-2,3-dihydro-1H-indole was prepared using 1-methyl-piperidin-4-one. M+H 290; Calc'd 289.4.
- b) 3,3-Dimethyl-1-(1-Boc-piperidin-4-ylmethyl)-6-nitro-2,3-dihydro-1H-indole using 1-Boc-4-formyl-piperidine.

15 **Preparation XXXIX - 3,3-Dimethyl-1-(1-methyl-piperidin-4-ylmethyl)-6-nitro-2,3-dihydro-1H-indole:**

3,3-Dimethyl-1-piperidin-4-ylmethyl-6-nitro-2,3-dihydro-1H-indole was treated with an excess of formaldehyde and $\text{NaBH}(\text{OAc})_3$ and stirred overnight at RT. The reaction was
20 quenched with MeOH and concentrated *in vacuo*. The residue was partitioned between EtOAc and 1 N NaOH. The organic layer was removed, washed with brine, dried (Na_2SO_4), filtered and concentrated to provide the compound.

25 **Preparation XL - (S) 2-(5-Nitro-2-pentafluoroethyl-phenoxy-methyl)-oxirane:**

Combined 5-nitro-2-pentafluoromethylphenol (2.69 g), DMF (25 mL) K_2CO_3 (3.03 g) and (S) toluene-4-sulfonic acid oxiranylmethyl ester (2.27 g) and stirred the mixture at 90 °C.
30 After about 4 h, the mix was cooled, diluted with EtOAc, washed with H_2O , 1 N NaOH (2x), 1 N HCl and then with brine. Dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purified the crude on silica gel column with 5% EtOAc/hexane

and drying under high vacuum provided the (S)-2-(5-nitro-2-pentafluoroethyl-phenoxy-methyl)-oxirane.

5 The following compounds were prepared similarly to the procedure outlined above:

a) (R)-2-(5-Nitro-2-pentafluoroethyl-phenoxy-methyl)-oxirane.

10 **Preparation XLI - (S) 2-Chloro-N-[3-(2-hydroxy-3-pyrrolidin-1-yl-propoxy)-4-pentafluoroethyl-phenyl]-nicotinamide:**

(S) 2-Chloro-N-[4-(2-oxiranylmethoxy)-3-pentafluoroethyl-phenyl]-nicotinamide (1.11 g) in a sealed tube and added pyrrolidine (285 μ L). Stirred after sealing tube at 60 °C. After 12 h, the mix was concentrated *in vacuo* and purified on a silica gel column (5:95:0.5 MeOH:CH₂Cl₂:NH₄OH - 8:92:1, MeOH:CH₂Cl₂:NH₄OH). Concentrated *in vacuo* and dried under high vacuum to obtain pure compound.

20 The following compounds were prepared similarly to the procedure outlined above:

a) (R) 1-(5-Nitro-2-pentafluoroethyl-phenoxy)-3-pyrrolidin-1-yl-propan-2-ol.

25 **Preparation XLII - 5-nitro-2-trifluoromethylanisole:**

Cooled 140 mL pyridine in a large sealable vessel to -40 °C. Bubbled in trifluoromethyl iodide from a gas cylinder which had been kept in freezer overnight. After adding ICF₃ for 20 min, added 2-iodo-5-nitroanisole (24.63 g) and copper powder (67.25 g). Sealed vessel and stirred vigorously for 30 22 h at 140 °C. After cooling to -50 °C, carefully unsealed reaction vessel and poured onto ice and Et₂O. Repeatedly washed with Et₂O and H₂O. Allowed the ice - Et₂O mixture to warm to RT. Separated layers, washed organic layer with 1N

HCl (3x), then brine, dried over Na₂SO₄, filtered and concentrated in vacuo. Eluted material through silica gel plug (4.5:1 Hex:CH₂Cl₂) to provide 5-nitro-2-trifluoromethylanisole.

5

Preparation XLIII - 1-[2-(5-nitro-2-trifluoromethylphenoxy)ethyl]pyrrolidine:

1-[2-(5-Nitro-2-trifluoromethylphenoxy)ethyl]-pyrrolidine was prepared from 5-nitro-2-trifluoromethyl-phenol and 1-(2-chloroethyl)pyrrolidine by a procedure similar to that described for 1-[2-(2-tert-butyl-5-nitro-phenoxy)-ethyl]-piperidine.

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Preparation XLIV - 1-[2-(5-Nitro-2-pentafluoroethyl-phenoxy)-ethyl]-piperidine:

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1-[2-(5-Nitro-2-pentafluoroethyl-phenoxy)-ethyl]-piperidine was prepared from 5-nitro-2-pentafluoroethylphenol and 1-(2-chloroethyl)piperidine by a procedure similar to that described in the preparation of 1-[2-(2-tert-butyl-5-nitro-phenoxy)-ethyl]-piperidine.

20

Preparation XLV - 3-(1-Boc-pyrrolidin-2-ylmethoxy)-4-pentafluoroethyl-phenylamine:

3-(2-Pyrrolidin-1-yl-methoxy)-4-trifluoromethyl-phenylamine was prepared from 1-[2-(5-nitro-2-trifluoromethylphenoxy)methyl]-pyrrolidine by a procedure similar to that described in the preparation of 1-Boc-4-(3-amino-5-trifluoromethyl-phenoxy)-piperidine.

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Preparation XLVI - 2-Chloro-N-[3-(2-pyrrolidin-1-yl-ethoxy)-4-trifluoromethyl-phenyl]-nicotinamide:

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2-Chloro-N-[3-(2-pyrrolidin-1-yl-ethoxy)-4-trifluoromethyl-phenyl]-nicotinamide was prepared from 3-(2-pyrrolidin-1-yl-ethoxy)-4-trifluoromethyl-phenylamine and 2-chloropyridine-

3-carbonyl chloride by a procedure similar to that described in the preparation of 1-Boc-4-{3-[(2-chloro-pyridine-3-carbonyl)-amino]-5-trifluoromethyl-phenoxy}-piperidine.

5 **Preparation XLVII - (R) Acetic acid 2-(5-nitro-2-pentafluoroethyl-phenoxy)-1-pyrrolidin-1-ylmethyl-ethyl ester:**

Dissolved 1-(5-nitro-2-pentafluoroethyl-phenoxy)-3-pyrrolidin-1-yl-propan-2-ol (3.5 g) in CH₂Cl₂ (15 mL), added
10 TEA (2.55 mL) and cooled to 0 °C. Acetyl chloride (781.3 μL) was added dropwise, forming a suspension. The mixture was warmed to RT and stirred for 1.5 h. Additional acetyl chloride (200 μL) was added and the mix was stirred for another h. The mixture was diluted with CH₂Cl₂ and washed
15 with sat. NaHCO₃. The organic layer was removed, washed with brine and back extracted with CH₂Cl₂. Dried the combined organic layers over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified over silica gel column (5:94.5:0.5 MeOH: CH₂Cl₂:NH₄OH) to provide acetic acid 2-(5-nitro-2-pentafluoroethyl-phenoxy)-1-pyrrolidin-1-ylmethyl-ethyl ester as a yellow brown oil.
20

The following compounds were prepared similarly to the procedure outlined above:

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- a) (R) Acetic acid 2-(5-amino-2-pentafluoroethyl-phenoxy)-1-pyrrolidin-1-yl-methyl-ethyl ester.
- b) 1-(2,2-Dimethyl-6-nitro-2,3-dihydro-benzo[1,4]oxazin-4-yl)-ethanone. M-NO₂ 206.4; Calc'd 250.1.

30

Preparation XLVIII - (R) 2-Chloro-N-[3-(2-hydroxy-2-pyrrolidin-1-yl-propoxy)-4-pentafluoroethyl-phenyl]-nicotinamide:

(R) Acetic acid 2-{5-[(2-chloro-pyridine-3-carbonyl)-amino]-2-pentafluoroethyl-phenoxy}-1-pyrrolidin-1-yl-ethyl ester (408 mg) was dissolved in MeOH (15 mL) and NH₄OH (6 mL) was added and the mixture was stirred at RT for 6 h. The reaction was concentrated *in vacuo* and dried under high vacuum. The residue was purified over silica gel column (8:92:0.6 MeOH: CH₂Cl₂:NH₄OH). The purified fractions were concentrated *in vacuo* and dried again to provide (R)-2-chloro-N-[3-(2-hydroxy-2-pyrrolidin-1-yl-ethoxy)-4-pentafluoroethyl-phenyl]-nicotinamide as a white foam.

Preparation XLIX - 2-Dimethylamino-1-(3,3-dimethyl-6-nitro-2,3-dihydro-indol-1-yl)-ethanone:

3,3-Dimethyl-6-nitro-2,3-dihydro-1H-indole (5 g) was dissolved in DMF (100 mL) and HOAt (3.89 g) dimethylamino-acetic acid (5.83 g) and EDC (3.89 g) were added. The reaction was stirred overnight. The mixture was diluted with CH₂Cl₂ (1 L) and washed with sat'd NaHCO₃ (3x200 mL). The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO₂, EtOAc to 5%MeOH/EtOAc) to afford the title compound.

The following compounds were prepared similarly to the procedure outlined above:

- a) 1-(3,3-Dimethyl-6-nitro-2,3-dihydro-indol-1-yl)-2-(N-Boc-amino)-ethanone.

Preparation L - 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-2-(N-Boc-amino)-ethanone:

1-(3,3-Dimethyl-6-nitro-2,3-dihydro-indol-1-yl)-2-(N-Boc-amino)-ethanone (3.9 g) was dissolved in EtOH (30 mL) and Fe powder (3.1 g) NH₄Cl (299 mg) and H₂O (5 mL) were added. The reaction was stirred at 80 °C overnight. The reaction was filtered through Celite® and evaporated off the MeOH. The residue was partitioned between CH₂Cl₂ and sat'd NaHCO₃. The organic layer was removed, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO₂, 25% EtOAc/hexane). The purified fractions were concentrated *in vacuo* to afford the compound as a white powder.

The following compounds were prepared similarly to the procedure outlined above:

- a) 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-2-dimethylamino-ethanone.
- b) 3,3-Dimethyl-1-(1-methyl-piperidin-4-ylmethyl)-2,3-dihydro-1H-indol-6-ylamine.
- c) 3-(4-Methyl-piperazin-1-ylmethyl)-4-pentafluoroethyl-phenylamine. M+H 324.2. Calc'd 323.
- d) 3,3-Dimethyl-1-(1-methyl-piperidin-4-yl)-2,3-dihydro-1H-indol-6-ylamine. M+H 259.6; Calc'd 259.3.
- e) 3,3-Dimethyl-1,1-dioxo-2,3-dihydro-1H-116-benzo[d]isothiazol-6-ylamine
- f) 1,1,4,4-Tetramethyl-1,2,3,4-tetrahydro-naphth-6-ylamine.
- g) 3,3-Dimethyl-1-(1-Boc-piperidin-4-ylmethyl)-2,3-dihydro-1H-indol-6-ylamine.

Preparation LI - 2-Boc-4,4-dimethyl-7-nitro-1,2,3,4-tetrahydro-isoquinoline:

4,4-Dimethyl-7-nitro-1,2,3,4-tetrahydro-isoquinoline (150 mg) was dissolved with CH_2Cl_2 (3 mL) DIEA (100 μL) DMAP (208 mg and Boc_2O (204 mg) and the mixture was stirred for 6 h at RT. The reaction was diluted with CH_2Cl_2 , washed with sat'd NaHCO_3 and dried over MgSO_4 , filtered and concentrated to provide the compound which was used without further purification.

10

The following compounds were prepared similarly to the procedure outlined above substituting Ac_2O :

a) 1-(4,4-Dimethyl-7-nitro-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone. $\text{M}+\text{H}$ 249.3.

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Preparation LII - 2-Bromo-N-(4-methoxy-benzyl)-5-nitro-benzamide:

PMB-amine (5.35 mL) in CH_2Cl_2 (130 mL) was slowly added to 2-bromo-5-nitro-benzoyl chloride (10.55 g) and NaHCO_3 (9.6 g) and the mixture was stirred at RT for 1 h. The mixture was diluted with CH_2Cl_2 (1 L), filtered, washed with dilute HCl , dried, filtered again, concentrated and dried under vacuum to provide the compound as a white solid. $\text{M}+\text{H}$ 367. Calc'd 366.

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Preparation LIII - 2-Bromo-N-(4-methoxy-benzyl)-N-(2-methyl-allyl)-5-nitro-benzamide:

To a suspension of NaH (1.22 g) in DMF (130 mL) was added 2-bromo-N-(4-methoxy-benzyl)-5-nitro-benzamide (6.2 g) in DMF (60 mL) at -78°C . The mixture was warmed to 0°C , 3-bromo-2-methyl-propene (4.57 g) was added and the mixture was stirred for 2 h at 0°C . The reaction was poured into ice H_2O , extracted with EtOAc (2x400 mL), dried over MgSO_4 ,

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filtered and concentrated to a DMF solution which was used without further purification.

Preparation LIV - of 2-(4-Methoxy-benzyl)-4,4-dimethyl-7-nitro-3,4-dihydro-2H-isoquinolin-1-one:

2-Bromo-N-(4-methoxy-benzyl)-N-(2-methyl-allyl)-5-nitro-benzamide (23.4 mmol) was dissolved in DMF (150 mL) and Et₄NCl (4.25 g), HCO₂Na (1.75 g) and NaOAc (4.99 g) were added. N₂ was bubbled through the solution for 10 min, then Pd(OAc)₂ (490 mg) was added and the mixture was stirred overnight at 70 °C. The mixture was extracted with EtOAc, washed with sat'd NH₄Cl, dried over MgSO₄, filtered and concentrated until the compound precipitated as a white solid.

The following compounds were prepared similarly to the procedure outlined above:

- a) 3,3-Dimethyl-6-nitro-2,3-dihydro-benzofuran was prepared from 1-bromo-2-(2-methyl-allyloxy)-4-nitro-benzene.
- b) 3,9,9-Trimethyl-6-nitro-4,9-dihydro-3H-3-aza-fluorene was prepared from 4-[1-(2-bromo-4-nitro-phenyl)-1-methyl-ethyl]-1-methyl-1,2,3,6-tetrahydro-pyridine.

Preparation LV - 4,4-Dimethyl-7-nitro-3,4-dihydro-2H-isoquinolin-1-one:

2-(4-Methoxy-benzyl)-4,4-dimethyl-7-nitro-3,4-dihydro-2H-isoquinolin-1-one (2.0 g) was dissolved in CH₃CN (100 mL) and H₂O (50 mL) and cooled to 0 °C. CAN (9.64 g) was added and the reaction was stirred at 0 °C for 30 min, then warmed to RT and stirred for 6 h. The mixture was extracted with CH₂Cl₂ (2 x 300 mL) washed with sat'd NH₄Cl, dried over MgSO₄, filtered and concentrated. The crude material was

recrystallized in $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ (1:1) to give 4,4-dimethyl-7-nitro-3,4-dihydro-2H-isoquinolin-1-one as a white solid.

Preparation LVI - 4,4-Dimethyl-7-nitro-1,2,3,4-tetrahydro-isoquinoline:

4,4-Dimethyl-7-nitro-3,4-dihydro-2H-isoquinolin-1-one (230 mg) was dissolved in THF (10 mL) and $\text{BH}_3\text{Me}_2\text{S}$ (400 μL) was added and the reaction was stirred overnight at RT. The reaction was quenched with MeOH (10 mL) and NaOH (200 mg) and heating at reflux for 20 min. The mixture was extracted with EtOAc, washed with sat'd NH_4Cl , extracted with 10% HCl (20 mL). The acidic solution was treated with 5 N NaOH (15 mL), extracted with EtOAc (30 mL) dried, filtered and evaporated to give the compound as a yellow solid. M+H 207.2, Calc'd 206.

The following compounds were prepared similarly to the procedure outlined above:

a) 4-Boc-2,2-dimethyl-6-nitro-3,4-dihydro-2H-benzo[1,4]oxazine.

Preparation LVII - 2-Bromomethyl-4-nitro-1-pentafluoroethyl-benzene:

2-Methyl-4-nitro-1-pentafluoroethyl-benzene (2.55 g) was dissolved in CCl_4 (30 mL) and AIBN (164 mg) and NBS (1.96 g) were added. The reaction was heated to reflux and stirred for 24 h. The mix was diluted with CH_2Cl_2 , washed with sat'd NaHCO_3 , dried over MgSO_4 and concentrated to give the compound as an oil which was used without further purification.

Preparation LVIII - 1-Methyl-4-(5-nitro-2-pentafluoroethyl-benzyl)-piperazine:

2-Bromomethyl-4-nitro-1-pentafluoroethyl-benzene (2.6 g) was added to N-methylpiperazine (5 mL) and stirred at RT for 3 h. The mixture was filtered and the filtrate was treated with 1-chlorobutane, extracted with 2 N HCl (100 mL). The acidic solution was treated with 5 N NaOH (6 mL) then extracted with EtOAc. The organic layer was removed, dried over MgSO₄ and concentrated to give the compound as an oil.

The following compounds were prepared similarly to the procedure outlined above:

a) 4-(5-Nitro-2-pentafluoroethyl-benzyl)-morpholine.

Preparation LIX - 1-Boc-4-(5-nitro-2-pentafluoroethyl-benzyl)-piperazine:

2-Bromomethyl-4-nitro-1-pentafluoroethyl-benzene (2.5 g) was dissolved in CH₂Cl₂ and added to N-Boc-piperazine (2.5 g) and NaHCO₃ (1 g) and stirred at RT overnight. The mixture was diluted with CH₂Cl₂ (100 mL), washed with sat'd NH₄Cl, dried over MgSO₄, filtered and concentrated. The residue was purified by silica gel chromatography (hexane, CH₂Cl₂:hexane 2:8) to give the compound as a yellow solid.

Preparation LX - (4-Boc-piperazin-1-yl)-(3-nitro-5-trifluoromethyl-phenyl)-methanone:

A mixture of 3-nitro-5-trifluoromethyl-benzoic acid (4.13 g), 4-Boc-piperazine (2.97 g), EDC (3.88 g), HOBT (2.74 g), DIEA (3.33 mL) in CH₂Cl₂ (120 mL) was stirred at RT for 3 h. The mixture was diluted with CH₂Cl₂ (100 mL), washed with sat'd NH₄Cl, dried over MgSO₄, filtered and concentrated. The residue was purified by silica gel chromatography

(hexane, CH₂Cl₂:hexane 1:2) to give the compound as a white solid.

Preparation LXI - 1-Boc-4-(3-nitro-5-trifluoromethyl-benzyl)-piperazine:

(4-Boc-piperazin-1-yl)-(3-nitro-5-trifluoromethyl-phenyl)-methanone (403 mg) was dissolved in THF (6 mL) and BH₃Me₂S (300 μL) was added and the reaction was stirred for 3 h at 60 °C and 2 h at RT. The reaction was quenched with MeOH (5 mL) and NaOH (100 mg) and stirred at RT for 1 h. The mixture was concentrated and dissolved in CH₂Cl₂, washed with sat'd NH₄Cl/NaHCO₃, dried (MgSO₄), filtered and evaporated to give the compound as an oil. M+H 390.3.

Preparation LXII - 2-Ethyl-4-aminomethyl pyridine:

To a solution of 2-ethyl-4-thiopyridylamide (10 g) in MeOH (250 mL) was added Raney 2800 Nickel (5 g, Aldrich) in one portion. The mixture was stirred at RT for 2 days then at 60 °C for 16 h. The mixture was filtered, concentrated to provide the desired compound.

Preparation LXIII - N-Boc-[2-(4-morpholin-4-yl-butyl)-pyrimidin-4-ylmethyl]-amine:

N-Boc-(2-chloropyrimidine)-methylamine (663 mg) and 4-(aminopropyl)morpholine (786 mg) were dissolved in MeOH and concentrated *in vacuo*. The residue was heated at 100 °C for 15 min, forming a solid which was dissolved in CH₂Cl₂/MeOH then concentrated again and heated 15 min more. Concentrated *in vacuo* and dried under high vacuum. Triturated with a small amount of IpOH and allowed to settle over a weekend. Filtered, rinsing with a small amount of IpOH to provide the compound as a white solid.

The following compounds were prepared similarly to the procedure outlined above:

- 5 a) (4-Bocaminomethyl-pyrimidin-2-yl)-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-amine. M+H 336.5; Calc'd 335.45.

Preparation LXIV - 2-fluoronicotinic acid:

10 In a flame dried 3-necked round bottom flask equipped with a dropping funnel and thermometer, under N₂, THF (250 mL) was added via cannula. LDA (2M in cyclohexane, 54 mL) was added via cannula as the flask was cooled to -78 °C. At -78 °C, 2-fluoropyridine (8.87 mL) was added dropwise over 10 min. The reaction was stirred for 3 h. Condensation was blown off (with N₂) a few cubes of solid CO₂ and they were added to
15 the mixture. The mixture was warmed to RT once the solution turned yellow, and it was stirred overnight. The reaction was cooled to 0 °C and the pH was adjusted to ~ 2.5 with 5N HCl. The mixture was concentrated in vacuo and extracted with EtOAc. The EtOAc layer was washed with brine, dried
20 over MgSO₄, filtered and concentrated to dryness. The resulting solid was slurried in EtOAc (100 mL), filtered, washed with cold EtOAc and dried at 50 °C for 1 h to afford 2-fluoronicotinic acid. M+H 142.1; Calc'd 141.0.

25 **Preparation LXV - 4-cyano-2-methoxypyridine:**

Under a stream of N₂ and with cooling, Na metal (2.7 g) was added to MeOH (36 mL) with a considerable exotherm. After the Na is dissolved, a solution of 2-chloro-4-cyanopyridine (15 g) in dioxane:MeOH (1:1, 110 mL) was added via dropping
30 funnel over a 10 min period. The reaction was heated to reflux for 3.5 h then cooled at ~ 10 °C overnight. Solid was filtered off and the solid was washed with MeOH. The filtrate was concentrated to ~ 60 mL and H₂O (60 mL) was added to redissolve a precipitate. Upon further

concentration, a precipitate formed which was washed with H₂O. Further concentration produced additional solids. The solids were combined and dried in vacuo overnight at 35 °C to provide 4-cyano-2-methoxypyridine which was used as is.

5

Preparation LXVI - (2-methoxypyridin-4-yl)methylamine:

4-Cyano-2-methoxypyridine (1.7 g) was dissolved in MeOH (50 mL) and conc. HCl (4.96 mL) was added. Pd/C (10%) was added and H₂ was added and let stand overnight. The solids were
10 filtered through Celite® and the cake was washed with MeOH (~ 250 mL). Concentration in vacuo produced an oil which was dissolved in MeOH (~ 20 mL). Et₂O (200 mL) was added and stirred for 1 h. The resulting precipitate was filtered and washed with Et₂O to afford (2-methoxypyridin-4-
15 yl)methylamine (HCl salt) as an off-white solid.

Preparation LXVII - 2-(4-Amino-phenyl)-2-methyl-propionic acid methyl ester:

2-Methyl-2-(4-nitro-phenyl)-propionic acid methyl ester (2.1
20 g) was dissolved in THF (70 mL) and AcOH (5 mL) and Zn (10 g) were added. The mixture was stirred for 1 h and filtered through Celite®. The filtrate was rinsed with EtOAc and the organics were evaporated to a residue which was purified on silica gel chromatography (40%EtOAc/hexanes) to provide the
25 desired compound as a yellow oil. M+H 194.

Preparation LXVIII - 1-(2-tert-Butyl-phenyl)-4-methyl-piperazine:

2-tert-Butyl-phenylamine and bis-(2-chloro-ethyl)-
30 methylamine were mixed together with K₂CO₃ (25 g), NaI (10 g) and diglyme (250 mL) and heated at 170 °C for 8 h. Cooled and filtered solid and evaporated solvent. Diluted with EtOAc, washed with NaHCO₃ solution, extracted twice

more with EtOAc, washed with brine, dried over Na₂SO₄ and evaporated to give the compound as a dark solid.

5 The following compounds were prepared similarly to the procedure outlined above:

a) 1-Bromo-2-(2-methyl-allyloxy)-4-nitro-benzene was prepared from methallyl bromide.

10 **Preparation LXIX 3-(1-Methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-5-trifluoromethyl-phenylamine:**

3-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-5-trifluoromethyl-phenylamine (8.8 g, 0.032 mmol) was added to trifluoromethanesulfonic acid 1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl ester (7.91 g, 0.032 mmol) and 2 N Na₂CO₃ aqueous solution (25 mL) was bubbled through N₂ for 5 min. Pd(PPh₃)₄ (3.7g, 3.2 mmol) was added and the reaction was heated to 80 °C for 16 h. The reaction was cooled to RT and diluted with Et₂O (100 mL). The mixture was filtered through Celite® and the
15 filtrate was washed with NaHCO₃ aqueous solution (25 mL) followed by brine (25 mL). The organic phase was dried over Na₂SO₄ and concentrated *in vacuo*. The desired compound was isolated by passing through silica gel column chromatography (EtOAc, then (2M NH₃) in MeOH/EtOAc) to provide a yellow
20 oil.
25

Preparation LXX - 3,3-Dimethyl-6-nitro-2,3-dihydro-benzo[d]isothiazole 1,1-dioxide:

3,3-Dimethyl-2,3-dihydro-benzo[d]isothiazole 1,1-dioxide was
30 added to KNO₃ in H₂SO₄ cooled to 0 °C and stirred for 15 min. The reaction was warmed to RT and stirred overnight. The mix was poured into ice and extracted with EtOAc (3x), washed with H₂O and brine, dried and evaporated to give the compound which was used without further purification.

The following compounds were prepared similarly to the procedure outlined above:

- 5 a) 1,1,4,4-Tetramethyl-6-nitro-1,2,3,4-tetrahydro-naphthalene

Preparation LXXI - 3-(1-Methyl-1,2,3,4-tetrahydro-pyridin-4-yl)-5-trifluoromethyl-phenylamine:

- 10 3-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-5-trifluoromethyl-phenylamine (1.2 g) was added to trifluoro-methanesulfonic acid 1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl ester (1.0 g), LiCl (500 mg, Aldrich), PPh₃ (300 mg, Aldrich) and 2 M Na₂CO₃ aqueous solution (6 mL) and was bubbled with N₂ for 5 min.
- 15 Pd(PPh₃)₄ (300 mg, Aldrich) was added and the reaction was heated to 80 °C for 16 h. The reaction was cooled to RT and diluted with Et₂O (100 mL). The mixture was filtered through Celite® and the filtrate was washed with NaHCO₃ aqueous solution (25 mL) followed by brine (25 mL). The
- 20 organic phase was dried over Na₂SO₄ and concentrated *in vacuo*. The desired compound was isolated by silica gel column chromatography (EtOAc 10% (2M NH₃) in MeOH/EtOAc) to provide yellow oil. M+H 257.2; Calc'd 256.1.

25 **Preparation LXXII - Trifluoromethylsulfonic acid 1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl ester:**

- In a three-necked round bottom flask equipped with a thermometer and an additional funnel was placed anhydrous THF (200 mL) and 2M LDA (82.8 mL). The solution was cooled
- 30 to -78 °C and a solution of 1-methyl-piperidin-4-one (20 mL) in anhydrous THF (70 mL) was added drop-wise. The reaction was warmed to -10°C over 30 min and cooled down again to -78 °C. Tf₂NPh (54.32 g) in 200 mL of anhydrous THF was added through the additional funnel over 30 min and anhydrous THF

(30 mL) was added to rinse the funnel. The reaction was warmed to RT and the reaction solution was concentrated in vacuo. The residue was dissolved in Et₂O purified on neutral Al₂O₃ column chromatography (Et₂O as elutant). The compound was obtained as orange oil. (20 g)

Preparation LXXIII - 3-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-5-trifluoromethyl-phenylamine:

N₂ was bubbled through a solution of 3-bromo-5-trifluoromethyl-phenylamine (2.38 g), 5,5,5',5'-tetramethyl-[2,2']bi[[1,3,2]dioxaborinanyl] (2.24 g, Frontier Scientific) and KOAc (2.92 g), dppf (165 mg, Aldrich) in anhydrous dioxane (50 mL) for 2 min. PdCl₂ (dppf) (243 mg, Aldrich) was added and the reaction was heated to 80 °C for 4 h. After cooling to RT, the mix was diluted with 50 mL of Et₂O, filtered through Celite®, and the filtrate was concentrated *in vacuo*. The residue was dissolved in Et₂O (100 mL), washed with sat. NaHCO₃ aqueous solution (50 mL) followed by brine (50 mL). The organic phase was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was dissolved in 3:2 Et₂O/Hex (100 mL), filtered through Celite® and the filtrate was concentrated *in vacuo* to afford a dark brown semi-solid.

Preparation LXXIV - 1-Boc-3-Hydroxymethyl-azetidine:

A solution of 1-Boc-azetidine-3-carboxylic acid (1.6 g) and Et₃N (2 mL) in anhydrous THF (60 mL) was cooled to 0 °C. Isopropyl chloroformate (1.3 g) was added via a syringe slowly; forming a white precipitate almost immediately. The reaction was stirred for 1 h at 0 °C and the precipitate was filtered out. The filtrate was cooled to 0 °C again and aqueous NaBH₄ solution (900 mg, 5 mL) was added via pipette and stirred for 1 h. The reaction was quenched with NaHCO₃ solution (50 mL) and the compound was extracted with EtOAc

(200 mL). The organic phase was washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in EtOAc and passed through a short silica gel pad. Concentrating the filtrate *in vacuo* provided the
5 compound as a light yellow oil.

Preparation LXXV - 1-Boc-3-(3-nitro-5-trifluoromethyl-phenoxy)methyl)-azetidine:

A mixture of 1-Boc-3-methylsulfonyloxymethyl-azetidine (1.47
10 g), 3-nitro-5-trifluoromethyl-phenol (1.15 g) and K_2CO_3 (1.15 g) in DMF (20 mL) at 80 °C was stirred overnight. The reaction was cooled to RT and diluted with 25 mL of sat. NaHCO_3 and 50 mL of EtOAc. The organic phase was separated and washed with brine (25 mL), dried over Na_2SO_4 and
15 concentrated *in vacuo*. The crude compound was purified by column chromatography (50% EtOAc/hex).

Preparation LXXVI - 2,2-Dimethyl-6-nitro-3,4-dihydro-2H-benzo[1,4]oxazine:

20 2,2-Dimethyl-6-nitro-4H-benzo[1,4]oxazin-3-one was added to BH_3 -THF complex (Aldrich) in THF with ice cooling. The mixture was heated to reflux for 2 h then carefully diluted with 12 mL of MeOH and heated to reflux for an additional 1 h. Concentrated HCl (12 mL) was added and heated to reflux
25 for 1 h. The mixture was concentrated and the resulting solid was suspended in a dilute aqueous solution of NaOH (1 M) and extracted with EtOAc (100 mL x 4). The organic layers were washed with H_2O and dried over MgSO_4 . Evaporation of solvent gave a yellow solid.

30

Preparation LXXVII - 2,2,4-Trimethyl-6-nitro-4H-benzo[1,4]oxazin-3-one:

2,2-Dimethyl-6-nitro-4H-benzo[1,4]oxazin-3-one (1.1 g) was mixed with MeI (850 mg, Aldrich), K_2CO_3 (1.38 g, Aldrich)

and DMF (30 mL, Aldrich) at 40 °C for 48 h. The DMF was removed *in vacuo* and the residue was diluted with EtOAc (80 mL). The organic phase was washed with H₂O (50 mL), aqueous Na₂SO₃ (50 mL) and brine (50 mL). The resulting solution
5 was dried (MgSO₄) and concentrated to provide the compound which was used as is.

Preparation LXXVIII - 2-Bromo-N-(2-hydroxy-5-nitro-phenyl)-2-methyl-propionamide:

10 2-Amino-4-nitro-phenol (3.08 g, Aldrich) was stirred with THF (30 mL, Aldrich) in an ice bath. 2-Bromo-2-methyl-propionyl bromide (2.47 mL, Aldrich) and Et₃N (2.0 g, Aldrich) was slowly added via syringe. The mixture was stirred for 45 min then poured into ice. The aqueous phase
15 was extracted by EtOAc (50 mL x 4). The organic layer was dried and concentrated. The desired compound was crystallized from EtOAc. (Chem. Pharm. Bull., 44(1):103-114 (1996)).

20 **Preparation LXXIX - 2,2-Dimethyl-6-nitro-4H-benzo[1,4]oxazin-3-one:**

2-Bromo-N-(2-hydroxy-5-nitro-phenyl)-2-methyl-propionamide was mixed with K₂CO₃ in 20 mL of DMF and stirred overnight at 50 °C. The reaction mixture was poured into ice H₂O.
25 The precipitate was collected by filtration and washed with H₂O. The crude compound was recrystallized from EtOH.

Preparation LXXX -4-[1-(2-Bromo-4-nitro-phenyl)-1-methyl-ethyl]-1-methyl-pyridinium iodide:

30 1-Methyl-4-[1-methyl-1-(4-nitro-phenyl)-ethyl]-pyridinium (8 g) was dissolved in glacial HOAc (10 mL) then diluted with H₂SO₄ (50 mL), then NBS (3.8 g) was added. After 1 h, additional NBS (1.2 g) was added, 30 min later another 0.5 g of NBS, then 15 min later 200 mg more NBS. After 1 h, the

mixture was neutralized with NH_4OH (conc.) with ice bath cooling. The neutralized mixture was then concentrated and used as is.

5 **Preparation LXXXI - 4-[1-(2-Bromo-4-nitro-phenyl)-1-methyl-ethyl]-1-methyl-1,2,3,6-tetrahydro-pyridine:**

4-[1-(2-Bromo-4-nitro-phenyl)-1-methyl-ethyl]-1-methyl-pyridiniumiodide was mixed with MeOH (400 mL) and CH_2Cl_2 (200 mL), then treated with NaBH_4 (2.5 g) in portions.
10 After stirring at RT for 2 h, the mixture was extracted with CH_2Cl_2 (300 mL x 3). The CH_2Cl_2 layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*, to provide the desired compound.

15 **Preparation LXXXII - 1-Methyl-4-[1-methyl-1-(4-nitro-phenyl)-ethyl]-pyridinium iodide:**

4-(4-Nitro-benzyl)-pyridine (4.3 g) was mixed with MeI (4 mL, 9.12 g)/NaOH (5 N, 30 mL), Bu_4NI (150 mg) and CH_2Cl_2 (50 mL) and stirred at RT overnight. Additional MeI (2 mL) was
20 added along with 50 mL of NaOH (5N). 6 h later, more MeI (2 mL) was added. The mixture was stirred at RT over the weekend. The mixture was cooled on ice bath and the base was neutralized by conc. HCl (aq) addition dropwise to pH 7. The compound was used as is.

25

Preparation LXXXIII - 1-Methyl-4-(4-nitro-benzyl)-1,2,3,6-tetrahydro-pyridine:

4-(4-Nitrobenzyl)pyridine (64 g) and TBAI (6 g) were dissolved in CH_2Cl_2 (500 mL) and the solution was suspended
30 with NaOH (aq. 5N, 450 mL) in a 3L 3-necked round bottom flask. With vigorous stirring, CH_3I (213 g) was added and stirred vigorously at RT for 60 h (or until blue color disappears). The reaction was quenched with dimethylamine (100 mL) and MeOH (300 mL) and stirred for 2 h. NaBH_4 (19

g) was added to the mixture in small portions. The reaction mixture was stirred for 30 min at RT, then partitioned between $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (500 mL/500 mL). The organic layer was collected and the aqueous layer was washed with CH_2Cl_2 (300 mL x 3). The combined organic layers was washed with brine then concentrated in vacuo. The residue was purified on a silica wash-column (7% TEA in EtOAc). The desired fractions were combined and concentrated under vacuum to give the desired compound as a dark gray solid. (MS: $M+1=261$).

Preparation LXXXIV - 1-Boc-4-formylpiperidine:

4A Molecular sieves were heated to 100 °C and a vacuum was applied. They were cooled to RT and purged with N_2 . CH_2Cl_2 (420 mL) and CH_3CN (40 mL), NMO (40 g) and 1-Boc-4-hydroxymethylpiperidine (50 g) were added and the mix was stirred for 5 min then cooled to 15 °C. TPAP (4.1 g) is added and an exotherm was observed. The reaction was maintained at RT with external cooling. The reaction was stirred at RT for 3 h, filtered, concentrated, diluted with 50% EtOAc/hexanes and purified on a silica gel plug (50%EtOAc/hexanes). The eluant fractions were concentrated to afford a yellow oil.

Preparation LXXXV - 2-Chloro-4-cyanopyridine:

2-Chloro-4-cyanopyridine was prepared similar to the method described by Daves et al., J. Het. Chem., 1:130-132 (1964).

Preparation LXXXVI - 4-(2-tert-Butyl-5-nitro-phenyl)-but-3-en-1-ol:

A mix of 1-(tert-butyl)-2-bromo-4-nitrobenzene (3.652 g), TEA (5.92 mL), 3-buten-1-ol (5.48 mL), $\text{Pd}(\text{OAc})_2$ (32 mg), $\text{Pd}(\text{PPh}_3)_4$ (327 mg) and toluene (40 mL) was degassed with nitrogen and heated in a sealed vessel for 16 h at 120 °C.

The next day, the reaction mixture was cooled to RT, filtered, and concentrated *in vacuo*. The crude was eluted on a silica gel column with 15% to 22% EtOAc/hexanes gradient system to yield a yellow-brown oil.

5

Preparation LXXXVII - 4-(2-tert-Butyl-5-nitro-phenyl)-but-3-enal:

4-(2-tert-Butyl-5-nitro-phenyl)-but-3-en-1-ol (1.024 g) was dissolved in 10 mL of CH₂Cl₂ and added dropwise over 5 min to a -78 °C mix of oxalyl chloride (0.645 mL), DMSO (0.583 mL), and 10 mL CH₂Cl₂. The reaction was stirred at -78 °C for 1 h, then treated with a solution of TEA (1.52 mL) in 7 mL CH₂Cl₂ and stirred at -78 °C for an additional 25 min, then warmed to -30 °C for 35 min. The reaction was treated with 50 mL of saturated aqueous NH₄Cl, diluted with H₂O and extracted with EtOAc. The organic layer was brine-washed, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to yield a yellow oil which was used as is in Preparation LXXXVIII.

20

Preparation LXXXVIII - 1-[4-(2-tert-Butyl-5-nitro-phenyl)-but-3-enyl]-pyrrolidine:

4-(2-tert-Butyl-5-nitro-phenyl)-but-3-enal (895 mg) was dissolved in 40 mL THF, and to the solution was added pyrrolidine (0.317 mL). To the deep orange solution was added NaBH(OAc)₃ (1.151 g) and glacial AcOH (0.207 mL). The reaction was stirred at RT overnight, then treated with saturated aqueous NaHCO₃ and diluted with Et₂O and some 1N NaOH. The layers were separated, and the organic layer was extracted with aqueous 2 N HCl. The acidic aqueous layer was basified to pH>12 with 6 N NaOH, extracted with Et₂O, brine-washed, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to provide 1-[4-(2-tert-butyl-5-nitro-phenyl)-but-3-enyl]-pyrrolidine as a orange-brown oil.

30

**Preparation LXXXIX - N-Boc-(2-chloropyrimidin-4-yl)-
methylaniline:**

To 2-chloropyrimidine-4-carbonitrile [2.5 g, prepared by the
5 procedure of Daves et. al. [J. Het. Chem., 1:130-132 (1964)]
in EtOH (250 mL) under N₂ was added Boc₂O (7.3 g). After
the mixture was briefly placed under high vacuum and flushed
with N₂, 10% Pd/C (219 mg) was added. H₂ was bubbled through
the mixture (using balloon pressure with a needle outlet) as
10 it stirred 4.2 h at RT. After filtration through Celite®,
addition of 1.0 g additional Boc₂O, and concentration, the
residue was purified by silica gel chromatography (5:1 →
4:1 hexanes/EtOAc) to obtain N-Boc-(2-chloropyrimidin-4-yl)-
methylaniline.

15

**Preparation XC - Methanesulfonic acid 1-Boc-azetidin-3-
ylmethyl ester:**

To a solution of (1-Boc-azetidin-3-yl)-methanol (1.06 g, 5.7
mmol), TEA (1.18 mL, 8.52 mmol) in CH₂Cl₂ at 0 °C was added
20 MeSO₂Cl (0.53 mL, 6.82 mmol) via a syringe. The reaction
was warmed to RT over 2 h and stirring was continued at RT
for 2 h. The white solid formed was removed by filtration
and the filtrate was washed with 25 mL of H₂O. The organic
phase was dried over Na₂SO₄, and concentrated *in vacuo* to
25 afford yellow oil.

Preparation XCI - N-(2-bromo-5-nitrophenyl)acetamide:

2-Bromo-5-nitroaniline (10 g) was dissolved in 500 mL of
CH₂Cl₂, DIEA (6.6 g) was added to the mixture, followed by
30 DMAP (100 mg). The mixture was cooled to 0 °C in ice bath.
Acetyl chloride (4 g in 50 mL CH₂Cl₂) was added dropwise to
the reaction mixture. After the mixture was stirred at RT
over 3 h, extracted once with saturated NaHCO₃ solution and
once with brine, the resulting organic layer was dried over

MgSO₄, filtered and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel with 1:1 EtOAc:Hexane to 100% EtOAc to afford N-(2-bromo-5-nitrophenyl)acetamide as a white solid. MS: 258 (M-1).

5 Calc'd. for C₈H₇BrN₂O₃-259.06.

Preparation XCII - N-(2-bromo-5-nitrophenyl)-N-(2-methylprop-2-enyl)acetamide:

A suspension of 2 g NaH (95% powder) in anhydrous DMF (100
10 mL) was cooled to -78 °C, N-(2-bromo-5-nitrophenyl)acetamide (7 g) in dry DMF (50 mL) was added to the mixture under N₂ atmosphere. After the mixture was warmed to 0 °C, 3-bromo-2-methylpropene (7.3 g in 20 dry DMF) was added to the mixture. The mixture was stirred at RT overnight. The
15 mixture was poured into a container of ice and extracted between saturated NaHCO₃ solution and EtOAc. The resulting organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel with 7:2 hexane:EtOAc to
20 afford the title compound as a yellow gum. MS: 314 (M+1). Calc'd. for C₁₂H₁₃BrN₂O₃-313.15.

Preparation XCIII - 1-(3,3-dimethyl-6-nitro-2,3-dihydro-indol-1-yl)ethanone:

25 N-(2-Bromo-5-nitrophenyl)-N-(2-methylprop-2-enyl)acetamide (4.5 g) was dissolved in anhydrous DMF (50 mL), tetraethylammonium chloride (2.5 g), sodium formate (1.2 g), NaOAc (3 g) were added, and the resulting mixture was bubbled with N₂ gas for 10 min. Pd(OAc)₂ (350 mg) was added and the mixture
30 was heated at 80 °C under N₂ atmosphere overnight. After the mixture was concentrated in vacuo, it was partitioned between saturated NaHCO₃ solution and EtOAc, the resulting organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The crude material was purified by

flash chromatography on silica gel with 2:1 Hexane:EtOAc to afford the title compound as a yellow gum. MS: 235 (M+1). Calc'd. for $C_{12}H_{14}N_2O_3$ -234.25.

5 **Preparation XCIV - 3,3-dimethyl-6-nitroindoline:**

1-(3,3-Dimethyl-6-nitro-2,3-dihydro-indol-1-yl)ethanone (1.8 g) was dissolved in EtOH (50 mL), 12N HCl (50 mL) was added and the resulting mixture was heated at 70 °C overnight. After the mixture was concentrated *in vacuo*, it was
10 partitioned between saturated $NaHCO_3$ solution and EtOAc, the resulting organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a yellow solid. MS: 193 (M+1). Calc'd. for $C_{10}H_{12}N_2O_2$ -192.21.

15 **Preparation XCV - 1-Acetyl-6-amino-3,3-dimethylindoline**

1-(3,3-Dimethyl-6-nitro-2,3-dihydro-indol-1-yl)ethanone (250 mg) was dissolved in MeOH (20 mL), the mixture was bubbled with H_2 for 10 min. 10% Pd/C (50 mg) was added and the mixture was stirred under H_2 overnight. The mixture was
20 filtered through Celite® and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel with 1:1 EtOAc: CH_2Cl_2 to afford the title compound as a white crystalline material. MS: 205 (M+1). Calc'd. for $C_{12}H_{16}N_2O$ -204.27.

25

Preparation XCVI - 4-(1,1,2,2,3,3,4,4,4-nonafluorobutyl)phenylamine:

4-Nitro-(1,1,2,2,3,3,4,4,4-nonafluorobutyl)benzene was synthesized by a method analogous to that described by
30 Gregory, W. A. et al. (J. Med. Chem., 33(9): 2569-2578 (1990)). The mixture of the above nitro intermediate (1.0 mmol), iron powder (5.0 mmol) and NH_4Cl (0.7 mmol) in EtOH (3 mL) and H_2O (3 mL) was stirred for 4 h at 80 °C.

Filtration and concentration gave the crude title compound, which was used without further purification.

Preparation XCVII - 2-bromo-1-tert-butyl-4-nitrobenzene:

5 NBS (125.0 g, 697.5 mmol, 1.5 eq) was slowly added to a solution of TFA:H₂SO₄ (5:1, 750 mL) and *tert*-butyl-4-nitrobenzene (100.0 g, 558.0 mmol) at RT. The solution was stirred for 24 h and poured over 5 kg of ice. The resulting suspension was filtered and washed with a 1:1 MeOH:H₂O
10 solution (200 mL) and dried in a vacuum oven. MS (ES⁺): 258.1, 260.1 (M+H)⁺. Calc'd for C₁₀H₁₂BrNO₂: 257.0.

Preparation XCVIII - 4-(2-tert-butyl-5-nitrophenyl)pyridine:

To a solution of 2-bromo-1-*tert*-butyl-4-nitrobenzene (8.6 g, 33.3 mmol) and toluene (70 mL) in a 150 mL round bottom
15 flask, 4-pyridylboronic acid (4.5 g, 36.6 mmol, 1.1 eq), Pd(PPh₃)₄ (3.8 g, 3.3 mmol, 0.1 eq) and K₂CO₃ (13.8 g, 99.9 mmol, 3 eq) were added. The solution was stirred for 24 h at 80°C before cooling to RT. The solution was filtered
20 through a pad of Celite® and purified by silica flash chromatography (30% EtOAc/Hexanes). This afforded the desired compound as a yellow solid. MS (ES⁺): 257.2 (M+H)⁺; (ES⁻): 255.2 (M-H)⁻. Calc'd for C₁₅H₁₆N₂O₂: 256.1.

25 **Preparation XCIX - 4-(2-tert-butyl-5-nitrophenyl)-1-methylpyridinium:**

4-(2-*tert*-Butyl-5-nitrophenyl)pyridine (2.0 g, 7.8 mmol) was added to a round-bottom flask and dissolved in EtOH (10 mL). CH₃I (30 mL) was added to the flask which was placed in a 80
30 °C sand bath and heated to reflux. After 6 h, the solution was cooled to RT and the excess CH₃I and EtOH were stripped-off under reduced pressure resulting in the desired compound as a light brown solid. MS (ES⁺): 271.2 (M+H)⁺; (ES⁻): 269.2 (M-H)⁻. Calc'd for C₁₆H₁₉N₂O₂⁺: 271.1.

Preparation C - 4-tert-butyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)aniline:

4-(2-tert-Butyl-5-nitrophenyl)-1-methylpyridinium (2.1 g,
5 7.8 mmol, Step C) was added to a 100 mL round-bottom flask
and dissolved in a 10% H₂O/EtOH mixture. To the flask iron
dust (1.31 g, 23.4 mmol, 3 eq) and NH₄Cl (460 mg, 8.6 mmol,
1.1 eq) were added. The flask was placed in a 100 °C sand
10 bath and heated to reflux. After 2 h, the solution was
cooled to RT and filtered through a pad of Celite®. The
resulting solution was stripped down to a yellow solid and
redissolved in MeOH (20 mL, anhydrous). The solution was
cooled to 0 °C by placing it in an ice bath and slowly
adding NaBH₄ (450 mg, 11.7 mmol, 1.5 eq). After addition of
15 the NaBH₄, the solution was cooled to RT and stirred for 30
min. The solvent was stripped-off under vacuum and the solid
was redissolved in CH₂Cl₂ and filtered. The solution was
concentrated *in vacuo* to afford an amorphous clear yellow
solid. MS (ES+): 245.2 (M+H)⁺. Calc'd for C₁₆H₂₄N₂: 244.2.

20

**Preparation CI - [1-(4-amino-phenyl)-ethyl]carbamic acid
tert-butyl ester:**

A mixture of 1-(S)-1-(4-nitrophenyl)ethylamine hydrochloride
(2 g), Boc₂O (2.6 g) and NaHCO₃ (3 g) in MeOH/H₂O (1:1, 200
25 mL) was stirred at RT overnight. The reaction was extracted
with EtOAc twice then washed with H₂O followed by brine. The
organic layer was dried with Na₂SO₄ and evaporated under
reduced pressure to give the protected nitrophenyl
ethylamine. Boc-1-(S)-1-(4 nitrophenyl)ethylamine (1 g) was
30 hydrogenated by H₂ atmosphere in the presence of Pd/C (200
mg) to give Boc protected aniline (0.8 g). The intermediate
was deprotected with 4 N HCl/dioxane to give the title
compound as the HCl salt.

Preparation CII - 1-[2-(tert-butyl)-5-aminophenyl]-4-methylpiperazine:

A mixture of 2-t-butylaniline (5.4 g) and methylchlorethylamine hydrochloride (7 g) and K₂CO₃ (5 g) in NaI (2 g) in diglyme (150 m) was heated at 170 °C for 8 h. The reaction was filtered and the filtrate was evaporated under high vacuum. The residue was mixed with EtOAc (200 mL) and H₂O (200 mL) and extracted with EtOAc twice. The combined organic layer was washed with brine and dried over Na₂SO₄ and evaporated to give crude 1-[2-(tert-butylphenyl)-4-methylpiperazine. The crude 1-[2-(tert-butylphenyl)-4-methylpiperazine (260 mg) was stirred with H₂SO₄ (3 mL) at 0°C and HNO₃ (1.2 mL, 70%) was slowly added to the reaction. The reaction was warmed to RT, stirred for 30 min, poured on ice and basified with K₂CO₃ slowly. The solution was extracted with EtOAc three times, washed with H₂O, followed by brine, dried over Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatography to give 1-[2-(tert-butyl)-5-nitrophenyl]-4-methylpiperazine (260 mg), which was hydrogenated under H₂ atmosphere to give 1-[2-(tert-butyl)-5-aminophenyl]-4-methylpiperazine.

The following compounds were prepared similarly to the procedure outlined above:

a) 1-(5-aminophenyl)-4-methylpiperazine

Preparation CIII - 4-(tert-butyl)-2-(4-methylpiperazinyl)phenylamine:

A mixture of 1-(tert-butyl)-2-bromo-4-nitrobenzene (3 g) and N-methylpiperazine (8 g) was heated neat at 130 °C for 4 h. The residue was purified by column chromatography to give 1-[4-bromo-5-(tert-butyl)-2-nitrophenyl]-4-methylpiperazine,

which was hydrogenated to furnish 4-(tert-butyl)-2-(4-methylpiperazinyl)-phenylamine.

Preparation CIV - {2-[4-(tert-butyl)-2-

5 **aminophenoxy]ethyl}dimethylamine:**

DEAD (2.6 mL) was added to a mixture of 2-nitro-4-tert-butylphenol (2 g) and N,N-dimethylethanolamine (1.3 g) and Ph₃P (4 g) in THF (50 mL). The reaction was stirred at RT for 1 h, diluted with EtOAc (50 mL) and washed with 1 N HCl
10 twice. The aqueous layer was basified with NaHCO₃, extracted with EtOAc twice and washed with H₂O and brine. The organic layer was dried over Na₂SO₄ and evaporated to give {2-[4-(tert-butyl)-2-nitrophenoxy]ethyl}-dimethylamine. It was
hydrogenated under H₂ atmosphere to give {2-[4-(tert-butyl)-
15 2-aminophenoxy]ethyl}-dimethylamine.

The following compounds were prepared similarly to the procedure outlined above:

20 a) [2-(2-aminophenoxy)ethyl]-dimethylamine.

Preparation CV - 2-amino-5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinoline:

7-Nitro-2,3,4-trihydroisoquinolin-1-one (500 mg) was heated
25 in POCl₃ (10 mL) to reflux for 8 h. The mixture was evaporated, mixed with toluene and evaporated again. The residue was dissolved in THF, H₂NNH₂ (1 mL) was slowly added to the reaction and stirred for 2 h. The reaction was
evaporated, heated with HC(OEt)₃ (15 mL) at 115 °C for 2 h,
30 extracted with EtOAc and hydrogenated to give 2-amino-5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinoline.

Preparation CVI - tert-butyl 4-[(6-nitro-3,3-dimethylindolinyl)methyl]piperidinecarboxylate:

3,3-Dimethyl-6-nitroindoline (450 mg) was dissolved in 20 mL of dichloroethane, N-boc-4-formylpiperidine (750 mg) was
5 added to the mixture, followed by 2 g NaHB(OAc)₃ and 1 mL of glacial AcOH. The mixture was stirred at RT overnight. Saturated NaHCO₃ solution (20 mL) was added to the reaction mixture and stirred for 1 h. The resulting mixture was
10 separated by separation funnel, the organic layer was extracted once with saturated NaHCO₃ solution and once with brine. The resulting organic layer was dried over MgSO₄, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel with 9:1 Hexane:EtOAc to afford an orange oil. MS: 290 (M-99).
15 Calc'd. for C₂₁H₃₁N₃O₄ - 389.5.

Preparation CVII - 3,3-dimethyl-1-piperidin-4-ylmethyl-2,3-dihydro-1H-indol-6-ylamine:

tert-Butyl 4-[(6-nitro-3,3-dimethylindolinyl)-
20 methyl]piperidinecarboxylate (900 mg) was dissolved in 10 mL MeOH, the mixture was bubbled with H₂ for 10 min. 10% Pd/C (30 mg) was added and the mixture was stirred under H₂ overnight. The mixture was filtered through Celite® and concentrated *in vacuo*. The crude material was purified by
25 flash chromatography on silica gel with 1:1 Hexane:EtOAc to afford a colorless oil. MS: 360 (M+1). Calc'd. for C₂₁H₃₃N₃O₂ - 359.5.

Preparation CVIII - (2-chloro-(3-pyridyl))-N-(4-phenoxyphenyl)carboxamide:

2-Chloronicotinoyl chloride (9.15 g, 0.052 mmol) was added to a stirred solution of 4-phenoxyaniline (10 g, 0.054 mmol) and DIEA (10 mL, 0.057 mmol) in CH₂Cl₂ (100 mL) at RT. The mixture was stirred for 48 h before removal of solvent under

reduced pressure. The resulting residue was dissolved in EtOAc and washed several times with saturated NaHCO₃ aqueous solution and brine, respectively. The organic layer was dried over Na₂SO₄ and evaporated to leave a solid. This material was re-crystallized from EtOAc/Hexane mixture, followed by filtration and rinsing with Et₂O to give the desired compound as a white solid. MS m/z: 325 (M+1); 323 (M-1).

Preparation CIX - 1-(1-methyl(4-piperidyl))-6-nitroindoline:
6-Nitroindoline (5 g) was dissolved in 200 mL of dichloroethane. N-Methyl-4-piperidone (5 g) was added to the mixture, followed by NaHB(OAc)₃ (12 g) and 1 mL of glacial AcOH. The mixture was stirred at RT overnight. A saturated NaHCO₃ (200 mL) solution was added to the reaction mixture and stirred for 1 h. The resulting mixture was separated by separation funnel. The organic layer was extracted once with saturated NaHCO₃ solution and once with brine. The resulting organic layer was dried over MgSO₄, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel with 2:1 EtOAc:MeOH to afford orange oil. MS: 262 (M+1). Calc'd. for C₁₄H₁₉N₃O₂ - 261.3.

Preparation CX - 1-(1-methyl-4-piperidyl)indoline-6-ylamine:
1-(1-Methyl(4-piperidyl))-6-nitroindoline (3 g) was dissolved in 100 mL MeOH and the mixture was bubbled with H₂ for 10 min. 10% Pd/C (200 mg) was added and the mixture was stirred under H₂ overnight. The mixture was filtered through Celite® and concentrated *in vacuo* to afford light yellow oil. MS: 232 (M+1). Calc'd. for C₁₄H₂₁N₃ - 231.3.

Preparation CXI - N-(2-bromo-5-nitrophenyl)acetamide:

2-Bromo-5-nitroaniline (10 g) was dissolved in CH_2Cl_2 (500 mL), DIEA (6.6 g) was added to the mixture, followed by 100 mg of DMAP. The mixture was cooled to 0 °C in ice bath.

5 Acetyl chloride (4 g in 50 mL CH_2Cl_2) was added dropwise to the reaction mixture. After the mixture was stirred at RT over 3 h, and extracted once with saturated NaHCO_3 solution and once with brine. The resulting organic layer was dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude

10 material was purified by flash chromatography on silica gel with 1:1 EtOAc:Hexane to 100% EtOAc to afford a white solid. MS: 258 (M-1). Calc'd. for $\text{C}_8\text{H}_7\text{BrN}_2\text{O}_3$ - 259.1.

Preparation CXII - N-(2-bromo-5-nitrophenyl)-N-(2-methylprop-2-enyl)acetamide:

15 A suspension of NaH (2 g) (95% powder) in 100 mL anhydrous DMF was cooled to -78 °C, and N-(2-bromo-5-nitrophenyl)acetamide (7 g) in 50 mL dry DMF was added to the mixture under N_2 . After the mixture was warmed to 0 °C,

20 3-bromo-2-methylpropene (7.3 g in 20 dry DMF) was added to the mixture. The mixture was stirred at RT overnight. The mixture was poured into a container of ice and extracted between saturated NaHCO_3 solution and EtOAc. The resulting organic layer was dried over MgSO_4 , filtered and

25 concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel with 7:2 Hexane:EtOAc to afford a yellow gum. MS: 314 (M+1). Calc'd. for $\text{C}_{12}\text{H}_{13}\text{BrN}_2\text{O}_3$ - 313.1.

Preparation CXIII - 1-(3,3-dimethyl-6-nitro-2,3-dihydro-indol-1-yl)ethanone:

30 N-(2-Bromo-5-nitrophenyl)-N-(2-methylprop-2-enyl)acetamide (4.5 g) was dissolved in 50 mL anhydrous DMF, 2.5 g tetraethyl-ammonium chloride, 1.2 g sodium formate, 3 g

sodium acetate were added, the resulting mixture was bubbled with N₂ gas for 10 min. Pd(OAc)₂ (350 mg) was added and the mixture was heated at 80 °C under N₂ overnight. After the mixture was concentrated in vacuo, it was extracted between
5 saturated NaHCO₃ solution and EtOAc, the resulting organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel with 2:1 Hexane:EtOAc to afford a yellow gum. MS: 235 (M+1). Calc'd. for C₁₂H₁₄N₂O₃ - 234.2.

10

Preparation CXIV - 3,3-dimethyl-6-nitroindoline:

1-(3,3-Dimethyl-6-nitro-2,3-dihydro-indol-1-yl)ethanone (1.8 g) was dissolved in 50 mL EtOH, 50 mL 12N HCl was added and the resulting mixture was heated at 70 °C overnight. After
15 the mixture was concentrated in vacuo, it was extracted between saturated NaHCO₃ solution and EtOAc. The resulting organic layer was dried over MgSO₄, filtered and concentrated in vacuo to afford a yellow solid. MS: 193 (M+1). Calc'd. for C₁₀H₁₂N₂O₂ - 192.2.

20

Preparation CXV - 3,3-dimethyl-1-(4-methyl-piperazin-1-yl)-6-nitro-2,3-dihydro-1H-indole:

3,3-Dimethyl-6-nitroindoline (0.8 g) was dissolved in 50 mL of dichloroethane, N-methyl-4-piperidone (1 g) was added to
25 the mixture, followed by 2.5 g NaHB(OAc)₃ and 1 mL of glacial AcOH. The mixture was stirred at RT overnight. Saturated NaHCO₃ solution (50 mL) was added to the mixture and stirred for 1 h. The resulting mixture was separated by separation funnel, the organic layer was extracted once with
30 saturated NaHCO₃ solution and once with brine, the resulting organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel with 9:1 EtOAc:MeOH to

afford an orange oil. MS: 290 (M+1). Calc'd. for $C_{16}H_{23}N_3O_2$ - 289.4.

Preparation CXVI - 3,3-dimethyl-1-(1-methyl(4-piperidyl))indoline-6-ylamine:

3,3-Dimethyl-1-(4-methyl-piperazin-1-yl)-6-nitro-2,3-dihydro-1H-indole (600 mg) was dissolved in 20 mL MeOH, the mixture was bubbled with H_2 for 10 min. 10% Pd/C (100 mg) was added and the mixture was stirred under H_2 . The mixture was filtered through Celite® and concentrated *in vacuo* to afford an oil. MS: 260 (M+1). Calc'd. for $C_{16}H_{25}N_3$ - 259.4.

Preparation CXVII - 3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-5-nitro-1H-indole:

5-Nitroindole (2.6 g) was dissolved in 100 mL anhydrous MeOH, followed by 5 g N-methyl-4-piperidone and NaOMe (5 g) powder. The mixture was heated to reflux under N_2 overnight. The mixture was concentrated *in vacuo*, and was extracted between saturated $NaHCO_3$ solution and EtOAc. The resulting organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a yellow solid. This solid was washed with 5 mL EtOAc and 2 mL MeOH to afford a bright yellow solid. MS: 258 (M+1). Calc'd. for $C_{14}H_{15}N_3O_2$ - 257.29.

Preparation CXVIII - 3-(1-methyl-4-piperidyl)indole-5-ylamine:

3-(1-Methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-5-nitro-1H-indole (2.7 g) was dissolved in 50 mL MeOH, the mixture was bubbled with H_2 for 10 min. 10% Pd/C (150 mg) was added and the mixture and stirred under H_2 overnight. The mixture was filtered through Celite® and concentrated *in vacuo* to afford a yellow oil. MS: 230 (M+1). Calc'd. for $C_{14}H_{19}N_3$ - 229.3.

Preparation CXIX - {3-[3-amino-5-(trifluoromethyl)phenyl]propynyl}dimethylamine:

A mixture of 3-bromo-5-trifluoromethylaniline (1.4 g, 5.9 mmol), 1-dimethylamino-2-propyne (1.3 mL, 0.76 mmol),
5 PdCl₂(PPh₃)₂ (0.26 g, 0.29 mmol) and CuI (114 mg, 0.60 mmol) in 10 mL of TEA was heated at 100 °C in a sealed tube for 3 h. The resulting mixture was filtered over Celite®. The filtrate was concentrated, and the residue was purified by prep-HPLC (reverse phase) to give the aniline. MS (ES+):
10 243 (M+H)⁺; (ES-): 241 (M-H)⁻. Calc'd C₁₂H₁₃F₃N₂ - 242.24.

Preparation CXX - {3-[3-amino-5-(trifluoromethyl)phenyl]propyl}dimethylamine:

A mixture of {3-[3-amino-5-(trifluoromethyl)-phenyl]propyl} dimethylamine (7 g, 29 mmol) and Pd(OH)₂ (0.5 g) in 250 mL
15 of MeOH was stirred under 50 psi H₂. After 2 h, the resulting mixture was filtered over Celite®. The filtrate was concentrated, and the residue was diluted with aq. 1 N HCl. The aq. layer was washed with Et₂O, made basic with
20 aq. 5 N NaOH, and extracted with CH₂Cl₂. The organic solution was dried over Na₂SO₄ and concentrated to give the titled compound. MS (ES+): 386 (M+H)⁺; (ES-): 384 (M-H)⁻. Calc'd C₁₈H₁₉ClF₃N₃O - 385.8.

25 **Preparation CXXI - 4,4,5,5-tetramethyl-2-(1-methyl(4-1,2,5,6-tetrahydropyridyl))-1,3,2-dioxaborolane:**

To a solution of LiHMDS (25 mL, 25 mmol, 1.0 M in THF) in 35 mL of THF was added 1-methyl-4-piperidinone (3.0 mL, 25 mmol) at -78 °C. The resulting solution was stirred for 2 h,
30 then Tf₂NPh (8.9 g, 25 mmol) was added. The resulting solution was warmed to RT and stirred for 2 h. The mixture was concentrated, and the residue was purified by alumina (neutral) chromatography to give 1-methyl-4-(1,2,5,6-tetrahydro)pyridyl-(trifluoromethyl) sulfonate. A mixture

of above triflate (5.0 g, 20 mmol), bis(pinacolato)diboron (5.6 g, 22 mmol), potassium acetate (6.5 g, 66 mmol), PdCl₂dppf (0.44 g, 0.6 mmol), and (dppf)₂ (0.33 g, 0.6 mmol) in 60 mL of dioxane was heated at 80 °C for 4 h. The resulting mixture was cooled to RT, diluted with Et₂O (150 mL). The ethereal solution was washed with H₂O followed by brine. The organic layer dried over Na₂SO₄, concentrated, and recrystallized in hexane-Et₂O to give the title intermediate.

10

Preparation CXXII - 5-(1-methyl(4-1,2,5,6-tetrahydropyridyl))-3-(trifluoro-methyl)phenylamine:

To a mixture of 4,4,5,5-tetramethyl-2-(1-methyl(4-1,2,5,6-tetrahydropyridyl))-1,3,2-dioxaborolane (1.0 g, 4.4 mmol), PdCl₂pddf (0.16 g, 0.2 mmol) and K₂CO₃ (1.8 g, 13.2 mmol) and 3-amino-5-bromobenzotrifluoride (0.8 g, 3.3 mmol) in DMF (25 mL) was heated at 80 °C for 16 h. The resulting mixture was diluted with EtOAc, washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by SiO₂ chromatography to give the title intermediate. MS (ES⁺): 257 (M+H)⁺. Calc'd C₁₃H₁₅F₃N₂ - 256.3.

20

Preparation CXXIII - 4-phenylpiperidine:

4-Cyano-4-phenylpiperidine HCl (10.0 g, 45.0 mmol) was combined with KOH pellets and stirred vigorously under Ar at 160 °C for 4 h. The reaction mix was cooled to RT and dissolved into toluene (100 mL) and H₂O (100 mL). After separation of the layers, the aqueous layer was back-extracted two times with toluene. The combined organic layer was dried over Na₂SO₄, concentrated *in vacuo*, and dried under high vacuum, yielding a white solid.

30

Preparation CXXIV - 1-methyl-4-phenylpiperidine:

To a stirring mixture at RT of 4-phenylpiperidine (5.24 g, 32.48 mmol) in CH₃CN (95 mL) was added a 37% solution of HCHO in H₂O (13 mL). To this mixture was added NaCNBH₃ (3.27 g, 51.97 mmol). AcOH was added dropwise every 10 min over the next h to maintain the reaction pH near 7. The reaction volume was then reduced *in vacuo*. The reaction mix was diluted with CH₂Cl₂ and washed with 2 N NaOH and then brine. The crude was concentrated *in vacuo* and eluted through a silica gel column with 10% MeOH/CH₂Cl₂. The 1-methyl-4-phenylpiperidine was concentrated *in vacuo*, yielding a clear oil.

Preparation CXXV - 4-(1-methyl-4-piperidyl)phenylamine:

To 1-methyl-4-phenylpiperidine (2.663 g, 15.19 mmol) was added carefully H₂SO₄ (15.2 mL). The reaction was cooled in an ice bath and a solution of H₂SO₄ (1.66 mL) and fuming HNO₃ (0.67 mL, 15.95 mmol) was added dropwise over 45 min. The mix was stirred at 0°C for 3 h then at RT for 1.5 h before being poured over about 90 g ice and basified with 24 g solid NaOH. The mix was extracted with CH₂Cl₂. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated *in vacuo*. The crude was eluted on a silica gel column with a MeOH/CH₂Cl₂ gradient to yield 1-methyl-4-(4-nitrophenyl)piperidine which was hydrogenated under H₂ to furnish the title compound.

Preparation CXXVI - 1-piperidylprop-2-en-1-one:

To a 0°C solution of acryloyl chloride (4.576 g, 50.558 mmol) in CH₂Cl₂ (50 mL) was added dropwise and very carefully piperidine (4.305 g, 50.558 mmol). The reaction flask was vented during the exothermic addition. After the addition was completed, the white slurry was stirred at 0 °C for 40 min and at RT for 1 h. The reaction was diluted with

70 mL CH_2Cl_2 and washed first with about 60 mL 2 N HCl and then with about 60 mL of a mix of 2N NaOH and brine. The organic layer was dried over Na_2SO_4 . The solution was evaporated by heating in a H_2O bath at 60 °C without vacuum.

5 Once most solvent had been evaporated off, dried the clear oil under high vacuum at RT for 30 min.

Preparation CXXVII - 1-(tert-butyl)-2-bromo-4-nitrobenzene:

Bromine (17.4 mL) was added dropwise over 40 min to a
10 stirred mixture of 4-tert-butyl nitrobenzene (59.5 g, 332 mmol), silver(II)sulfate (56.5 g, 181 mmol), H_2SO_4 (300 mL), and H_2O (33 mL) at RT. The mixture was stirred for a further 3 h and then poured into 0.1 M $\text{Na}_2\text{S}_2\text{O}_5/\text{H}_2\text{O}$ (1L). The solid was filtered, washed with H_2O , Et_2O , and CH_2Cl_2 .
15 The filtrate layers were separated. The aqueous fraction was extracted with Et_2O . The combined organic layers were combined, dried over Na_2SO_4 , and concentrated *in vacuo*. The yellow solid was triturated with hexanes to give a pale yellow crystalline solid.

20

Preparation CXXVIII - (2E)-3-[2-(tert-butyl)-5-nitrophenyl]-1-piperidylprop-2-en-1-one:

1-(tert-Butyl)-2-bromo-4-nitrobenzene (6.885 g, 26.674 mmol), 1-piperidylprop-2-en-1-one (4.827 g, 34.677 mmol),
25 and TEA (7.44 mL, 53.35 mmol) were dissolved in toluene (70 mL). To this solution was added $\text{Pd}(\text{OAc})_2$ (60 mg, 0.267 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (617 mg, 0.5335 mmol). The mix was degassed with N_2 and heated in a sealed vessel at 120 °C for 15 h. The reaction mixture was cooled to RT, filtered, and
30 concentrated *in vacuo*. The dark crude oil was eluted through a silica gel column with 15% to 22% EtOAc/hexanes gradient system to yield a thick amber oil as the title compound.

Preparation CXXIX - 3-(5-amino-2-tert-butylphenyl)-1-piperidin-1-yl-propenone:

(2E)-3-[2-(tert-Butyl)-5-nitrophenyl]-1-piperidylprop-2-en-1-one (3.22 g, 10.177 mmol) was dissolved in dioxane (20 mL) and IpOH (40 mL). To the N₂-degassed solution was added Pd/C 10% by weight catalyst (2 g). The mix was placed in a Parr hydrogenator and stirred for 18 h under 60 psi H₂. The reaction was not complete the next day, so the reaction was continued for an additional 20 h with fresh catalyst. The mix was filtered through Celite® and concentrated *in vacuo* to give a foamy oil.

Preparation CXXX - 4-(tert-butyl)-3-(3-piperidylpropyl)phenylamine:

3-(5-Amino-2-tert-butylphenyl)-1-piperidin-1-yl-propenone (2.312 g, 7.619 mmol) was dissolved in THF (100 mL) at RT. To this solution was added LiAlH₄ (434 mg, 11.43 mmol). After the reaction stopped exotherming, it was heated at reflux at about 80 °C for 4 h. The reaction mix was cooled to 0 °C and treated by dropwise addition of 0.458 mL H₂O, 0.730 mL 10% aqueous NaOH, and 1.19 mL H₂O, respectively. The mix was stirred at RT for 1 h. After 40 min about 3 g of Na₂SO₄ was added. The mix was filtered through Celite® and concentrated *in vacuo*. The crude was eluted through silica gel column with a gradient system of 95:5 to 90:10 CH₂Cl₂/MeOH, to yield an amber thick oil as the title compound.

The following compounds were prepared similarly to the procedure outlined above:

- a) 3-((1E)-4-Pyrrolidinylbut-1-enyl)-4-(tert-butyl)phenylamine.
- b) 4-(tert-Butyl)-3-(3-pyrrolidinylpropyl)phenylamine.

- c) 4-(tert-Butyl)-3-(3-morpholin-4-ylpropyl)phenylamine.
d) 3-[3-(4-methylpiperazinyl)propyl]phenylamine.
e) 4-[3-(4-methylpiperazinyl)propyl]phenylamine.

5

Preparation CXXXI - 3-(3-nitrophenyl)-1-(4-methylpiperazinyl)propan-1-one:

A slurry consisting of CH_2Cl_2 (15 mL), 3-nitrocinnamic acid (3.154 g, 16.329 mmol), 1-methylpiperazine (1.487 g, 14.845 mmol) and EDC (3.557 g, 18.556 mmol) were stirred at RT for 60 h. The reaction was diluted with H_2O and EtOAc. The aqueous layer was back-extracted with EtOAc. The combined organic layers were washed with 2 N NaOH and then brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The crude was eluted through a silica gel column with 5% MeOH/ CH_2Cl_2 , to yield an off-white solid, mostly trans-olefin compound.

Preparation CXXXII - 3-(3-aminophenyl)-1-(4-methylpiperazinyl)propan-1-one:

To a nitrogen-degassed solution of 3-(3-nitrophenyl)-1-(4-methylpiperazinyl)propan-1-one (3.67 g, 13.330 mmol, Step A) in MeOH (50 mL) was added 10% by weight Pd/C (500 mg). The mix was stirred under H_2 atmosphere for 18 h then filtered through Celite® and concentrated *in vacuo*, yielding a thick amber oil which eventually solidified into a dark pink solid.

The following compounds were prepared similarly to the procedure outlined above:

- a) 4-[3-(4-methylpiperazinyl)-3-oxopropyl]phenylamine.

Preparation CXXXIII - 1-(2-morpholin-4-ylethyl)indol-6-ylamine:

K₂CO₃ (5.08 g, 36.726 mmol) was added to a slurry of 6-nitroindole (1.985 g, 12.242 mmol), 4-(2-chloroethyl)
5 morpholine HCl (2.278 g, 12.242 mmol), and CH₃CN (100 mL). The mix was heated to reflux for 18 h, then cooled to RT, filtered, and concentrated *in vacuo*. The crude was eluted through a silica gel column with a gradient of 3:97 to 5:95 and finally 8:92 MeOH/CH₂Cl₂, to yield upon drying the
10 desired intermediate which was hydrogenated under conditions previously described.

Preparation CXXXIV - methyl 2-methyl-2-(4-nitrophenyl)propanoate:

15 To a stirred solution of 2-(4-nitrophenyl)propionic acid (9 g, 46 mmol, 1 eq) in MeOH (300 mL) was added HCl (4 M in Dioxane, 11.5 mL, 46 mmol, 1 eq). The mixture was stirred at RT overnight and was quenched with aqueous NaHCO₃. The mixture was extracted with EtOAc. The organic layer was
20 dried over MgSO₄ and evaporated under reduced pressure and the partial residue (4.34 g, 20.7 mmol, 1eq) at 0 °C in THF (100 mL) was added NaH (1.66 g, 41.5 mmol, 2 eq). Mixture was stirred at RT for 1h and CH₃I (2.58 g, 41.5 mmol, 2 eq) was added. Reaction was stirred at RT overnight and was
25 quenched with H₂O. Mixture was extracted with EtOAc. The organic layer was dried over MgSO₄ and evaporated under reduced pressure and used for the next step without further purification to give title compound.

30 Preparation CXXXV - 3-methyl-3-(4-nitrophenyl)butan-1-one:

To a stirred solution of methyl 2-methyl-2-(4-nitrophenyl)propionate (5.32 g, 23.8 mmol) in THF (200 mL) at 0 °C was added a solution of 1M BH₃ in THF (25.8 mL, 45.8 mmol). The reaction was stirred at RT overnight and was quenched with

MeOH. THF was evaporated under reduced pressure and the residue was diluted in EtOAc and aqueous HCl (1 M) was added. The mixture was extracted with EtOAc, the organic layer was dried over MgSO_4 and evaporated under reduced pressure. Purification by flash chromatography using 40% EtOAc-hexane gave a yellow solid. To the yellow solid (2.08 g, 10.8 mmol) at 0 °C in CH_2Cl_2 was added NMO (1.9 g, 16.1 mmol), molecular sieves 4 Å and TPAP (76 mg, 0.2 mmol). The reaction was stirred for 1h and filtered on a silica pad. Solvent was evaporated under reduced pressure, forming the crude aldehyde which was used as is. To a suspension of methoxymethyltriphenylphosphonium chloride (6.4 g, 18.6 mmol) in THF (150 mL) was added a solution of KHMDS 0.5 M in toluene (37 mL, 18.5 mmol). The mixture was stirred for 30 min and crude aldehyde was added. The reaction was stirred at RT for 1h and quenched with H_2O . The mixture was extracted with EtOAc, dried and evaporated under reduced pressure. Et_2O was added and a precipitate formed, which was filtered on a silica pad and rinsed with 40% EtOAc-hexane. The solvent was removed and crude material was dissolved in CH_2Cl_2 . A solution of TFA- H_2O (1:1, 10 mL) was added and the reaction was stirred for 2 h at RT. Aqueous NaHCO_3 was added until pH 7 and the mixture was extracted with CH_2Cl_2 . The organic layer was dried, filtered and evaporated. Crude compound was purified by flash chromatography (40% EtOAc-hexane) to give the title compound as a yellow oil.

Preparation CXXXVI - 4-(1,1-dimethyl-3-morpholin-4-ylpropyl)phenylamine:

To a stirred solution of 3-methyl-3-(4-nitrophenyl)butan-1-one (509 mg, 2.4 mmol) and morpholine (0.21 mL, 2.4 mmol) in THF (30 mL) was added $\text{NaBH}(\text{OAc})_3$ (0.73 g, 3.4 mmol). The mixture was stirred at RT overnight and washed with HCl

(1M). CH_2Cl_2 was added and the layers were separated. The aqueous layer was basified to pH 9 using NaOH 1M and extracted with CH_2Cl_2 . The organic layer was dried and evaporated the nitro compound. To a solution of the nitro compound (0.50 g, 1.8 mmol) in THF (40 mL) was added AcOH (1.97 mmol, 34.5 mmol) followed by zinc (9.1 g, 137 mmol). The mixture was stirred for 1 h, filtered on Celite®, diluted with H_2O and aqueous NaHCO_3 , and the THF layer was evaporated. The residue was extracted with EtOAc, dried and evaporated to give the title compound.

Preparation CXXXVII - 4-{2,2,2-trifluoro-1-[2-(2-methoxy)ethoxy]-1-(trifluoromethyl)ethyl}phenylamine:

Diethyl azodicarboxylate (366 mg, 2.1 mmol) was added dropwise to a solution of 2-(4-aminophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (520 mg, 2 mmol), 2-(2-methoxyethoxy)ethan-1-ol (240 mg, 2 mmol) and PPh_3 (550 mg, 2.1 mmol) in THF (10 mL). The mixture was stirred for 2 h, then partitioned between EtOAc and aqueous NaHCO_3 solution. The organic phase was washed with brine. After concentration in vacuo, the organic residue was purified by flash chromatography on silica to give the compound. MS: 362 (M+1). Calc'd. for $\text{C}_{14}\text{H}_{17}\text{F}_6\text{NO}_3$ - 361.29.

Preparation CXXXVIII - 2-fluoropyridine-3-carbonyl chloride:

To a solution of 2-fluoropyridine (10 g, 100 mmol) in THF (150 mL) under -78°C was added an LDA solution (2 M in heptane/THF/ethylbenzene, 60 mL) dropwise. The mixture was stirred at -78°C for 3 h, then was quenched with a stream of dry CO_2 . After warming to RT, the mixture was partitioned between EtOAc (100 mL) and H_2O (200 mL). The aqueous layer was acidified to pH between 3-4, and extracted with EtOAc. The organic solution was collected and washed with brine and dried over Na_2SO_4 . After removing the

solvent in vacuum, 2-fluoropyridine-3-carboxylic acid was obtained as a brown oil. MS: 140 (M-H). Calc'd. for $C_6H_4FNO_2$ - 141.10. 2-Fluoropyridine-3-carboxylic acid (7 g) was suspended in $SOCl_2$ (100 mL). After heating under reflux
5 for 2 h, the mixture became homogeneous. Access $SOCl_2$ was removed in vacuo to afford a brown solid as desired compound.

Preparation CXXXIX - N-(3-Amino-5-chloro-phenyl)-2-dimethylamino-acetamide:

To a solution of 5-chloro-benzene-1,3-diamine (3 g, 21 mmol) and dimethylamino-acetic acid (2.2 g, 21 mmol) in CH_2Cl_2 (300 mL) was added EDC (5 g, 25 mmol), HOBt (2.9 g, 21 mmol), and DIEA (5 mL). The reaction mixture was stirred at
15 RT for overnight. Solvent was removed in vacuum and the residue was purified through flash chromatography on silica gel (0-8% MeOH in EtOAc) to give the desired compound.

Preparation CXL - 2-amino-4-nitro-benzamide:

To a solution of 2-amino-4-nitro-benzoic acid (9.1 g, 50 mmol) in CH_2Cl_2 (500 mL) was added EDC (12 gram, 60 mmol), HOBt (6.8 g, 50 mmol), DIEA (12 mL), and NH_3 in MeOH (2 M, 40 mL). The reaction was stirred at RT for overnight, and a precipitation formed. The solid was isolated via vacuum
25 filtration.

Preparation CXLI - 6-nitro-3H-quinazolin-4-one:

2-Amino-4-nitro-benzamide was suspended in triethyl orthoformate (50 mL) and the mixture was heated to 140 °C
30 for 5 h. Excess reagent was removed in vacuum. The residue was washed in hexanes to give the compound as a yellow solid.

Preparation CXLII - 6-amino-3H-quinazolin-4-one:

Hydrogenation of 6-nitro-3H-quinazolin-4-one (2 g) in EtOH (200 mL) was catalyzed by Pd/c (10%, 200 mg) under a H₂ balloon for 1 h. MeOH (200 mL) was added to the mixture.

- 5 The suspension was filtered through a layer of Celite® and the filtrate was concentrated in vacuum to give the desired compound.

Preparation CXLIII - (2,4-dinitro-phenyl)-acetic acid methyl ester:

- 10 To a solution of (2,4-dinitro-phenyl)-acetic acid (5 g) in MeOH (100 mL) was added concentrated H₂SO₄ (1 mL) and the resulting solution was heated at reflux for overnight. After removing solvent in vacuum, the residue was
- 15 partitioned between EtOAc and aqueous NaHCO₃ (sat.). The organic solution was concentrated in vacuum to give the desired compound which was used without further purification.

Preparation CXLIV - 6-amino-1,3-dihydro-indol-2-one:

- 20 An EtOH solution of (2,4-dinitro-phenyl)-acetic acid methyl ester was treated with H₂ balloon and catalyzed with Pd/c (10%, 500 mg) at RT. The resulting mixture was filtered through a layer of Celite® and concentrated in vacuum to
- 25 afford the desired compound.

Preparation CXLVI - 3-Methyl-but-2-enoic acid (6-bromopyridin-2-yl)-amide:

- 30 To a solution of 2-amino-6-bromopyridine (3.015 g, 0.017 mmol) and Et₃N (2.40 mL, 0.017 mmol) in CH₂Cl₂ (20.0 mL), was added 3,3-dimethylacryloylchloride (1.96 mL, 0.017 mmol) under N₂ at 0 °C. The mixture was slowly warmed to RT and stirred for 12 h. The reaction was quenched by the addition of H₂O (20.0 mL), the organic layer was separated, dried

over Na₂SO₄ and evaporated to dryness to yield crude compound which was used without purification.

Preparation CXLVI - 3-Methyl-but-2-enoic acid (6-amino-pyridin-2-yl)-amide:

To a solution of 3-methyl-but-2-enoic acid (6-bromo-pyridin-2-yl)-amide (4.30 g, 0.017 mmol) and copper (0.214 g, 3.372 mmol) in IpOH (20.0 mL), was added NH₄OH (20.0 mL) in a sealed vessel under N₂. The reaction was sealed and heated to 90 °C for 12 h. The reaction mixture was cooled to RT and EtOAc (50.0 mL) was added. The organic layer was separated, and then the aq layer was washed with EtOAc (50.0 mL). Combined organic layers were evaporated to dryness, the resulting residue was dissolved in CH₂Cl₂ (50.0 mL) and washed with H₂O (4 x 30 mL). The organic layer was dried over Na₂SO₄ and evaporated to dryness to yield crude aminopyridine which was used without purification.

Preparation CXLVII - 7-Amino-4,4-dimethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one:

To a mixture of aminopyridine (1.12 g, 5.833 mmol) and AlCl₃ (3.11 g, 0.023 mmol) was added chlorobenzene (10.0 mL) in a sealed vessel under Ar. The reaction was sealed and heated to 120 °C for 12 h. The reaction mixture was cooled to RT and the mixture was poured over ice/HCl mixture and extracted with EtOAc (3 x 50.0 mL). The aqueous layer was neutralized via addition of solid NaHCO₃ and extracted with EtOAc (5 x 50 mL). Combined organic layers were dried over Na₂SO₄ and evaporated to dryness to yield crude compound. Chromatography (Silica gel, CH₂Cl₂:MeOH, 99:1) yielded pure naphthyridin.

Preparation CXLVIII - 2-[1-(3-Amino-phenyl)-2,2,2-trifluoro-1-trifluoromethyl-ethoxymethyl]-pyrrolidine-1-carboxylic acid tert-butyl ester:

To a mixture of 2-(3-amino-phenyl)-1,1,1,3,3,3-hexafluoro-
5 propan-2-ol (1.30 g), 2-hydroxymethyl-pyrrolidine-1-
carboxylic acid tert-butyl ester (1.04 g), PPh₃ (2.64 g) and
molecular sieves 4 Å in THF (100 mL) was added diethyl
diazocarboxylate (1.55 mL) slowly. The reaction was stirred
at RT for 4 h and at reflux for overnight. After filtration
10 to remove solids, the filtrate was concentrated and the
residue was taken into Et₂O. The organic phase was washed
with saturated NaHCO₃ and brine. The organic layer was
dried over MgSO₄ and evaporated to give a crude compound as
very viscous brown oil, which was purified by chromatography
15 through silica gel (500 g, 30% to 50% EtOAc in hexanes) to
afford 2-[1-(3-amino-phenyl)-2,2,2-trifluoro-1-
trifluoromethyl-ethoxymethyl]-pyrrolidine-1-carboxylic acid
tert-butyl ester as a light brown oil.

20 **Preparation CXLIX - Pyrimidine-4-carbaldehyde oxime:**

9.14 g (97.11 mmol) of 4-methylpyrimidine was slowly added
to a 0°C solution of 8.75 g HCl in 40 mL EtOH. To this
white suspension was added, over 5 min, 61 mL of a 10-20% by
weight solution of ethyl nitrite in EtOH. The reaction was
25 stirred at 0 °C for 10 min and then at RT for 2.5 h. The
white salt was filtered and dried under vacuum. The salt
was dissolved into 20 mL H₂O and very slowly treated with
about 200 mL saturated aqueous KHCO₃. A white solid
precipitated out of the purple solution. The solid was
30 filtered and dried under vacuum to yield the titled
compound.

Preparation CL - C-Pyrimidin-4-yl-methylamine dihydrogen chloride:

To a solution of 3.549 g (28.82 mmol) pyrimidine-4-carbaldehyde oxime in 200 mL MeOH was added after degassing
5 with Ar, 800 mg of 10% by weight Pd/C. The mix was stirred under H₂ for 4 h, then filtered through a Celite® plug. The solution was concentrated under vacuum to a volume of about 50 mL and then treated carefully with 30 mL of 4 N HCl in dioxane. The mix was concentrated and dried under vacuum to
10 yield the titled compound as a pink solid.

Preparation CLI - 2-(2,4-Dinitro-phenyl)-3,3,3-trifluoro-2-trifluoromethyl-propionic acid methyl ester:

A mixture of 7.08 g (38.07 mmol) 2,4-dinitrofluorobenzene,
15 2.43 g (41.88 mmol) KF, and 0.58 g (2.21 mmol) 18-crown-6-ether in 37 mL sulfolane was added 4.00 g (19.04 mmol) methyl 2-(trifluoromethyl)-3,3,3-trifluoropropionate dropwise over about 7 h via syringe pump. After the addition was complete, another 2.43 g KF, 0.58 g 18-Crown-6-
20 ether were added and then 4.00 g Methyl 2-(trifluoromethyl)-3,3,3-trifluoropropionate were added dropwise over 12 h. The next day, repeated additions using same amounts and setting syringe pump addition over 14 h. The following day, the additions were again repeated, this time using half the
25 amounts as above additions and setting syringe pump addition at 12 h. After addition was completed, the reaction mix was cooled to RT and diluted into Et₂O and 0.5 N aqueous HCl. The layers were separated, and the organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated
30 under vacuum. The crude was eluted on a silica gel column with EtOAc/hexanes gradient, to yield the titled compound, as a yellow solid. [See Vlasov et al., J. Org. Chem. USSR (Engl. Trans.), 15:1953-1964 (1979)]

Preparation CLII - 6-Amino-1-hydroxy-3,3-bis-trifluoromethyl-1,3-dihydro-indol-2-one:

To an argon-degassed solution of 5.13 g (13.64 mmol) 2-(2,4-dinitro-phenyl)-3,3,3-trifluoro-2-trifluoromethyl-propionic acid methyl ester in 300 mL EtOH was added 0.5 g of 10% by weight Pd/C. The reaction was stirred under H₂ overnight and filtered through Celite®, concentrated down, and dried under vacuum, yielding the titled compound.

10 Preparation CLIII - 6-Amino-3,3-bis-trifluoromethyl-1,3-dihydro-indol-2-one:

To a solution of 1.245 g (4.151 mmol) 6-amino-1-hydroxy-3,3-bis-trifluoromethyl-1,3-dihydro-indol-2-one in 80 mL THF was added 3.565 mL (62.27 mmol) glacial AcOH and 19 g (290.6 mmol) Zinc dust (100 mesh). The reaction was stirred 40 min at RT and then 5 h at reflux. The reaction was cooled to RT. The solvent was decanted and concentrated, then dissolved in EtOAc and filtered through Celite®. The EtOAc solution was then washed with saturated aqueous NaHCO₃ and brine, dried over Na₂SO₄, filtered, and concentrated and dried under vacuum, to yield the titled compound, as a yellow solid.

25 Preparation CLIV - N-[3-(2-Amino-ethoxy)-4-pentafluoroethyl-phenyl]-2-chloro-nicotinamide:

To a solution of 500 mg (0.98 mmol) Boc-N-[3-(2-Amino-ethoxy)-4-pentafluoroethyl-phenyl]-2-chloro-nicotinamide in 10 mL CH₂Cl₂ was added 10 mL TFA and stirred for 2 h. The reaction was concentrated down, treated with 6N aqueous NaOH, and extracted 3 times with CH₂Cl₂. The combined organic extracts were dried over Na₂SO₄, filtered, concentrated down, and dried under vacuum, yielding the titled compound.

Preparation CLV - 2-Chloro-N-[3-(2-methanesulfonylamino-ethoxy)-4-pentafluoroethyl-phenyl]-nicotinamide:

To a solution of 381 mg (0.93 mmol) N-[3-(2-amino-ethoxy)-4-pentafluoroethyl-phenyl]-2-chloro-nicotinamide in 10 mL
5 CH₂Cl₂ at 0 °C was added 0.389 mL Et₃N and 0.072 mL (0.93 mmol) methanesulfonylchloride. After 5 min, the reaction was stirred at RT for 30 min. The reaction was diluted with CH₂Cl₂, washed with brine, dried over Na₂SO₄, filtered, concentrated, and dried under vacuum, yielding the titled
10 compound as a white foamy solid.

Preparation CLVI - 2-Methyl-2-(4-nitro-phenyl)-propionic acid:

To a solution of 2-(4-nitro-phenyl)-propionic acid (50 g, 0.26 mole) in 250 mL of MeOH was added 6 mL of concentrated
15 HCl. The resulting solution was heated at reflux for 16 h. Then the resultant mixture was diluted with 200 mL of aq. NaHCO₃ and 500 mL of EtOAc. The organic layer was separated, dried over Na₂SO₄, and concentrated. The residue
20 was diluted with 100 mL of THF and added to a suspension of NaH (11.2 g, 0.28 mole, 60% in mineral oil) in 600 mL of THF. To the resulting mixture was added CH₃I (18.3 mL, 0.29 mole) in one portion. The resulting mixture was stirred for 48 h at 40 °C, then was diluted with aq. NH₄Cl solution and
25 EtOAc. The organic layer was separated, dried over Na₂SO₄, and concentrated. The residue was used without further purification.

To a solution of the residue (54 g, 0.24 mole) in 500 mL of MeOH was added 5N aq. NaOH (144 mL, 0.72 mole). The
30 mixture was stirred for 16 h at 40 °C. The resulting mixture was concentrated, the residue was diluted with H₂O (500 mL), and acidified with 2 N HCl to give a precipitate. The precipitate was filtered and dried to give the titled

compound as a yellowish solid. MS: 210 (M+1), Calc'd for $C_{10}H_{12}NO_4$ - 210.20.

Preparation CLVII - 2-Methyl-5-[1-methyl-1-(4-nitro-phenyl)-ethyl]-[1,3,4]oxadiazole:

5 A mixture of 2-methyl-2-(4-nitro-phenyl)-propionic acid (5 g, 24 mmol.) and a few drops of DMF in $SOCl_2$ was stirred at reflux for 16 h. The resulting solution was concentrated to give corresponding acid chloride as a brown solid.

10 To a mixture of the acid chloride (2.33 g, 10.2 mmol), acetic acid hydrazide (0.91 g, 12.2 mmol.), Et_3N (2.86 mL, 20.2 mmol.) in CH_2Cl_2 (50 mL) was added 2 crystals of DMAP at RT. The mixture was stirred for 16 h and concentrated. A solution of the residue in 50 mL of phosphorous oxychloride

15 was heated at 95 °C for 16 h. The mixture was concentrated and diluted with ice-water and EtOAc. The organic layer was washed with saturated aq. $NaHCO_3$ solution twice, dried over Na_2SO_4 , and concentrated. The residue was purified by SiO_2 chromatography (hexane: EtOAc=1:1) to give the titled

20 compound as a pale yellow crystal. MS: 248 (M+1), Calc'd for $C_{12}H_{14}N_3O_3$ -248.10.

Preparation CLVIII - 2-Methyl-5-[1-methyl-1-(4-amino-phenyl)-ethyl]-[1,3,4]oxadiazole:

25 A mixture of 2-methyl-5-[1-methyl-1-(4-nitro-phenyl)-ethyl]-[1,3,4]oxadiazole (1.36 g, 5.5 mmol) and Pd/C (68 mg) in EtOAc (50 mL), was stirred under 1 atm of H_2 for 16 h. The resultant was filtered over Celite®, and the filtrate was concentrated to give the titled compound as a pale yellow

30 crystalline. MS: 218 (M+1) calc'd for $C_{12}H_{16}N_3O$ -218.12.

Preparation CLIX - 4-[1-Methyl-1-(4-nitro-phenyl)-ethyl]-pyrimidine:

To a mixture of 1-(4-nitro-phenyl)-propan-2-one (5.32 g, 29.7 mmol), triethylbenzylammonium chloride (0.34g, 1.5 mmol), and 13 mL of aq. 5N KOH solution (65.3 mmol) in CH_2Cl_2 was added CH_3I (4.06 mL, 65.3 mmol). The resulting mixture was stirred at 40 °C, and then diluted with EtOAc and H_2O . The organic layer was dried and concentrated. To the residue (1.0 g, 4.8 mmol) in toluene (30 mL) was added dimethylformamide dimethylacetal (1.27 mL, 9.6 mmol). The resulting mixture was heated at reflux for 6 h then concentrated to give 1-dimethylamino-4-methyl-4-(4-nitro-phenyl)-pent-1-en-3-one as a yellow solid (MS 263 (M+1) Calc'd for $\text{C}^{14}\text{H}_{19}\text{N}_2\text{O}_3$ -263.13).

A mixture of 1-dimethylamino-4-methyl-4-(4-nitro-phenyl)-pent-1-en-3-one (0.5 g, 1.9 mmol.), formamidine HCl (0.305 g, 3.8 mmol), and NaOEt (1.29 g, 4.0 mmol) was heated in Smith synthesizer under microwave for 10 min at 150 °C. The resultant mixture was diluted with H_2O and EtOAc. The organic layer was dried, and the residue was used without further purification. MS: 244 (M+1) Calc'd for $\text{C}_{13}\text{H}_{14}\text{N}_3\text{O}_2$ -244.10.

Preparation CLX - 5-[1-Methyl-1-(4-nitro-phenyl)-ethyl]-1H-pyrazole:

A mixture of 1-dimethylamino-4-methyl-4-(4-nitro-phenyl)-pent-1-en-3-one (0.36 g, 1.4 mmol) and hydrazine hydrate (1.0 g, 6.25 mmol) in EtOH was heated at 50 °C for 3h. The mixture was concentrated, and the residue was diluted with H_2O and EtOAc. The organic layer was dried over Na_2SO_4 and concentrated to give the titled compound as a yellow solid. MS: 232 (M+1) Calc'd for $\text{C}_{12}\text{H}_{14}\text{N}_3\text{O}_2$ -232.10.

Preparation CLXI - 2-tert-Butyl-5-nitro-phenylamine:

Concentrated H_2SO_4 (1 L) was cooled to $-10\text{ }^\circ\text{C}$ with a dry ice
IpOH bath in a 2 L 3-neck round bottom flask fitted with a
mechanical stirrer and temperature probe. 2-*t*-Butylaniline
5 (109 g, 730 mmol) was added, giving a clumpy solid. Once
the temperature of the mixture was stabilized at $-10\text{ }^\circ\text{C}$,
 KNO_3 (101 g, 1001 mmol) was added portion-wise, as the
solid, over 4 h, maintaining the temperature between -20 and
 $-5\text{ }^\circ\text{C}$. Once all of the KNO_3 was added, the reaction was
10 stirred overnight with gradual warming to RT. The reaction
was quenched by diluting with H_2O and extracting 3x with
EtOAc. The EtOAc extracts were washed multiple times with
saturated $\text{NaHCO}_3(\text{aq})$, until gas evolution ceased, then with
brine. The EtOAc extracts were combined, dried over
15 anhydrous Na_2SO_4 , filtered and concentrated under reduced
pressure giving a black oil. The oil was eluted through a
36 x 7 cm column of silica gel with a 5%; 10%; 15%; 25%; and
50% EtOAc:Hexanes step gradient (2 L each step) giving 2-
tert-butyl-5-nitro-phenylamine as a red solid.

20

Preparation CLXII - 2-Bromo-N-(2-tert-butyl-5-nitro-phenyl)-acetamide:

2-tert-Butyl-5-nitro-phenylamine (70 g, 359 mmol) and a
catalytic amount of DMAP were dissolved in THF (1.5 L) under
25 N_2 . TEA (109 g, 1077 mmol) was added and the solution was
cooled to $0\text{ }^\circ\text{C}$. Bromoacetyl bromide (207 g, 1023 mmol) was
added and the reaction was gradually warmed to RT with
stirring overnight. The reaction was partially concentrated
under reduced pressure, treated with H_2O and extracted with
30 EtOAc (3x). The EtOAc extracts were washed with brine,
combined, dried over anhydrous Na_2SO_4 , filtered and
concentrated under reduced pressure giving a black oil.
This oil was eluted through a 38 x 7 cm column of silica gel

with 95:5:0.5 CH₂Cl₂:MeOH:NH₄OH_(aq) eluant giving 2-bromo-N-(2-tert-butyl-5-nitro-phenyl)-acetamide as a brown solid.

Preparation CLXIII - N-(2-tert-Butyl-5-nitro-phenyl)-2-dimethylamino-acetamide:

2-Bromo-N-(2-tert-butyl-5-nitro-phenyl)-acetamide (80 g, 253 mmol) and K₂CO₃ (70 g, 506 mmol) were combined in a 3-L 3-neck round bottom flask fitted with a mechanical stirrer, N₂ inlet, and pressure equalizing addition funnel. THF (1.75 L) was added and the mixture was cooled to 0 °C under N₂. DMA (400 mL of a 2 M solution in THF, 800 mmol) was added to the mixture through the pressure equalizing addition funnel over 30 min. The mixture was gradually warmed to RT with stirring overnight. The reaction was quenched by filtering it under vacuum and then concentrating the filtrate under reduced pressure. The recovered material was eluted through a 36 x 7 cm column of silica gel with 50% EtOAc:Hexanes giving N-(2-tert-butyl-5-nitro-phenyl)-2-dimethylamino-acetamide as a brown solid.

The pyrrolidino and morpholino analogs are prepared by substituting the dimethylamine with respectively pyrrolidine or morpholine and using the same chemistry as described.

a) N-(2-tert-Butyl-5-nitro-phenyl)-2-pyrrolidin-1-yl-acetamide.

b) N-(2-tert-Butyl-5-nitro-phenyl)-2-morpholin-4-yl-acetamide.

Preparation CLXIV - N-(5-Amino-2-tert-butyl-phenyl)-2-dimethylamino-acetamide:

N-(2-tert-Butyl-5-nitro-phenyl)-2-dimethylamino-acetamide (25.8 g, 92 mmol) was dissolved in EtOH (1.4 L) and 1,4-

dioxane (200 mL). The solution was degassed under vacuum with stirring. 10% Pd/C (2.5 g) was added (as a slurry in EtOH). The mixture was degassed again, then the reaction vessel was charged with H₂ gas (balloon) and stirred
5 overnight at RT. The reaction was filtered through Celite® with MeOH and the filtrate was concentrated under reduced pressure. The recovered material was eluted through a 36 x 7 cm column of silica gel with a 97.5:2.5:0.25 and 95:5:0.5 CH₂Cl₂:MeOH:NH₄OH_(aq) step gradient giving N-(5-amino-2-tert-
10 butyl-phenyl)-2-dimethylamino-acetamide as a brown solid.

Preparation CLXV - 5-Chloro-1-methyl-1H-pyrazole-4-carboxylic acid (4-tert-butyl-phenyl)-amide:

5-Chloro-1-methyl-1H-pyrazole-4-carbonyl chloride (1.0 g,
15 5.6 mmol) was dissolved in CH₂Cl₂ (100 mL) under N₂ and cooled to 0 °C. 4-*t*-Butylaniline was added and the reaction was stirred with gradual warming to RT overnight. The reaction was quenched with saturated NaHCO₃(aq) and extracted 3 x with fresh CH₂Cl₂. The CH₂Cl₂ extracts were
20 washed with brine, combined, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure giving 5-chloro-1-methyl-1H-pyrazole-4-carboxylic acid (4-tert-butyl-phenyl)-amide as a foamy pink solid.

25 Preparation CLXVI - 1,2-dihydro-3-spiro-1'-cyclopropyl-1H-indole:

A solution of 3-(2-bromo-ethyl)-1H-indole (5 g) in anhydrous CH₃CN (100 mL) was suspended with oven dried K₂CO₃ (20 g) and heated to reflux for 10 h. After cooling to RT, the mixture
30 was filtered and the filter cake was washed with EtOH (50 mL). The combined filtrate was treated with NaBH₄ (300 mg) and stirred for 3 h at RT. Solvents were removed *in vacuo* and the residue was partitioned between H₂O (160 mL) and EtOAc (60 mL). The organic layer was extracted with aqueous

HCl (0.5 N, 30 mL X 2). The acid layer was basified with NH₄OH (aq. Conc.) and extracted with EtOAc. The organic phase was washed with brine and dried over Na₂SO₄ and concentrated to give the desired compound as a colorless thin oil.

Preparation CLXVII- 6-nitro-1,2-dihydro-3-spiro-1'-cyclopropyl-1H-indole:

1',2'-Dihydrospiro(cyclopropane-1,3'-[3H]indole) (1.8 g 12.4 mmol) was added in dropwise over a period of 20 min to a cooled (-5 to -10 °C) solution of NaNO₃ (1.3 g) in H₂SO₄ (conc., 30 mL). After the addition, the reaction was stirred for another 40 min., then the mixture was poured onto crushed ice (200 g) and the resulting mixture was basified with NH₄OH (aq., conc.) with cooling. The basified mixture was extracted with EtOAc twice and the organic layer was washed with brine then dried over Na₂SO₄. After concentration *in vacuo*, the compound was isolated as a dark gray solid.

Preparation CLXVIII - Ethyl 6-nitro-1,2-dihydro-3-spiro-1'-cyclopropyl-1H-indole-1-carbamate:

A solution of 6-nitro-1,2-dihydro-3-spiro-1'-cyclopropyl-1H-indole (2.7 g) in CH₂Cl₂ (100 mL) was suspended with NaHCO₃ (5 g), and ethyl chloroformate was added dropwise with vigorous stirring. After the addition, the reaction was stirred overnight. The mixture was washed with H₂O (100 mL), then dried over Na₂SO₄ and concentrated *in vacuo*. The residue was recrystallized in MeOH to give the title compound as a dark gray crystalline.

Preparation CLXIX - Ethyl 6-amino-1,2-dihydro-3-spiro-1'-cyclopropyl-1H-indole-1-carbamate:

Ethyl 6-nitro-1,2-dihydro-3-spiro-1'-cyclopropyl-1H-indole-1-carbamate (2.1 g) was dissolved in EtOH (200 mL),
5 suspended with Pd/C (10%, 560mg) and equipped with a balloon filled with H₂. The hydrogenation was finished in 3 h. The reaction mixture was filtered through a layer of Celite®. The filtrate was concentrated *in vacuo* to give the desired product as a white solid.

10

Preparation CLXX - 4-[1-Methyl-1-(4-nitro-phenyl)-ethyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid ethyl ester:

1-Methyl-4-[1-methyl-1-(4-nitro-phenyl)-ethyl]-1,2,3,6-tetrahydro-pyridine (5.2 g) was dissolved in toluene (100
15 mL) and ethyl chloroformate (2.4 g). The mixture was heated at reflux for overnight and cooled to RT. The toluene solution was washed with NaHCO₃ (aq., sat. 100 mL) then brine (100 mL) and dried over Na₂SO₄. The organic phase was concentrated *in vacuo* to give the desired compound which was
20 used without purification.

Preparation CLXXI - 4-[1-Methyl-1-(4-amino-phenyl)-ethyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid ethyl ester:

4-[1-Methyl-1-(4-nitro-phenyl)-ethyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid ethyl ester was dissolved in EtOH
25 (150 mL) and suspended with Pd/C (10%, 1g). The reaction flask was equipped with a balloon filled with H₂. The hydrogenation was continued for 3 days. The mixture was filtered through a layer of Celite® and concentrated *in vacuo* to provide the desired compound as a light brown oil.
30

Preparation CLXXII: 3,3-dimethyl-6-nitroindoline 3-Methyl-but-2-enoic acid (3-acetylamino-phenyl)-amide:

3,3-Dimethylacryloyl chloride (3.3 mL, 29.3 mmol) was added to a mixture of 3'-aminoacetanilide (4.40 g, 29.3 mmol) and Et₃N (4.5 mL, 32.2 mmol) in 50 mL of CH₂Cl₂ and 25 mL of THF at 0 °C under N₂. The mixture was stirred at RT overnight, diluted with 100 mL of CH₂Cl₂, washed with aqueous Na₂CO₃, then brine, condensed, and purified by flash column chromatography (15 to 30% of EtOAc in CH₂Cl₂). The titled compound was obtained as an off-white solid. MS (ES⁺): 233.1 (M+H)⁺. Calc'd for C₁₃H₁₆N₂O₂ - 232.28.

The following compounds were prepared similarly to the procedure outlined above:

a) 3-Methyl-but-2-enoic acid phenylamide. MS(ES⁺): 176.1 (M+H)⁺. Calc'd for C₁₁H₁₃NO - 175.23.

Preparation CLXXIII - N-(4,4-Dimethyl-2-oxo-1,2,3,4-tetrahydro-quinolin-7-yl)-acetamide:

The mixture of 3,3-dimethyl-6-nitroindoline 3-Methyl-but-2-enoic acid (3-acetylamino-phenyl)-amide (1.05 g, 4.52 mmol) and AlCl₃ (5.0 g, 37.5 mmol, Aldrich, 99.99%) in 50 mL of anhydrous chlorobenzene was stirred at 120 °C (oil bath temperature) under N₂ overnight, cooled to RT, poured into 10 mL of ice cold HCl, stirred for 30 min, and extracted with EtOAc. The organic portions were combined, washed with brine, dried with Na₂SO₄, filtered, condensed, and purified by flash column chromatography (1% of MeOH in CH₂Cl₂). The titled compound was obtained as an off-white solid. MS (ES⁺): 233.2 (M+H)⁺. Calc'd for C₁₃H₁₆N₂O₂ - 232.28.

The following compounds were prepared similarly to the procedure outlined above:

a) 4,4-Dimethyl-3,4-dihydro-1*H*-quinolin-2-one MS(ES^+): 175.6 (M+H) $^+$. Calc'd for $\text{C}_{11}\text{H}_{13}\text{NO}$ - 175.23.

5 **Preparation CLXXIV: 7-Amino-4,4-dimethyl-3,4-dihydro-1*H*-quinolin-2-one:**

N-(4,4-Dimethyl-2-oxo-1,2,3,4-tetrahydro-quinolin-7-yl)-acetamide (1.50 g, 6.46 mmol) in 10 mL of HCl (concentrated, 37%) and 30 mL of EtOH was stirred at 75 °C for 4 h. The solvents were removed under reduced pressure. The residue was dissolved in EtOAc/ H_2O , neutralized with NaHCO_3 , washed with brine, dried with Na_2SO_4 , filtered, and condensed to give the titled compound as an off-white solid. MS (ES^+): 191.2 (M+H) $^+$. Calc'd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}$ - 190.24.

15

Preparation CLXXV - 4,4-Dimethyl-1,2,3,4-tetrahydro-quinolin-7-ylamine:

The mixture of 7-amino-4,4-dimethyl-3,4-dihydro-1*H*-quinolin-2-one (1.07 g, 5.62 mmol) and borane dimethylsulfide complex (1.60 mL, 16.9 mmol) in 40 mL of anhydrous THF was heated at reflux under N_2 for 15 h. The solvents were removed under reduced pressure. The residue was heated at reflux in 20 mL of MeOH for 2 h, then 0.80 g of NaHCO_3 was added, and the mixture was heated at reflux for 2 h. The mixture was filtered, condensed, and the residue was purified by flash column chromatography (5 to 10% of EtOAc in CH_2Cl_2). The titled compound was obtained as a viscous oil. MS(ES^+): 176.9 (M+H) $^+$. Calc'd for $\text{C}_{11}\text{H}_{16}\text{N}$ - 176.26.

30 The following compounds were prepared similarly to the procedure outlined above:

a) 4,4-Dimethyl-1,2,3,4-tetrahydroquinoline MS(ES^+): 162.5 (M+H) $^+$. Calc'd for $\text{C}_{11}\text{H}_{15}\text{N}$ - 161.24.

Preparation CLXXVI - N-(4,4-Dimethyl-1,2,3,4-tetrahydro-quinolin-7-yl)-2-fluoronicotinamide:

The mixture of 4,4-dimethyl-1,2,3,4-tetrahydro-quinolin-7-ylamine (0.20g, 1.13 mmol), 2-fluoronicotinic acid (0.16g, 1.13 mmol), TBTU (0.36 g, 1.13 mmol), and DIEA (0.24 mL, 1.36 mmol) in 5 mL of DMF was stirred at RT for 3 h, then partitioned between EtOAc and Na₂CO₃ (aq). The organic layer was washed with H₂O, brine, dried with MgSO₄, filtered, condensed, and the residue was purified by flash column chromatography (20 to 30% of EtOAc in CH₂Cl₂). The titled compound was obtained as an off-white solid. MS (ES⁺): 300.1 (M+H)⁺. Calc'd for C₁₇H₁₈FN₃O- 299.34.

The following compounds were prepared similarly to the procedure outlined above:

a) N-(4,4-Dimethyl-2-oxo-1,2,3,4-tetrahydro-quinolin-7-yl)-2-fluoronicotinamide, as an off-white solid. MS (ES⁺): 314.2 (M+H)⁺. Calc'd for C₁₇H₁₆FN₃O₂- 313.33.

b) N-(1-Ethyl-4,4-dimethyl-1,2,3,4-tetrahydro-quinolin-7-yl)-2-fluoronicotinamide, MS(ES⁺): 328.3 (M+H)⁺. Calc'd for C₁₉H₂₂FN₃O - 327.40.

Preparation CLXXVII - 4,4-Dimethyl-7-nitro-1,2,3,4-tetrahydro-quinoline:

To 13 mL of H₂SO₄ (96%) cooled in a salt ice bath was added dropwise 4,4-dimethyl-1,2,3,4-tetrahydro-quinoline (5.80 g, 36.0 mmol). The resulting slurry was stirred for 30 min, upon when concomitant addition of HNO₃ (90%, 1.70 mL, 36.0 mmol) and H₂SO₄ (96%, 7 mL) was started, the addition was finished in 20 min, the mixture was stirred at 0 °C to 15 °C for 2 h, poured into ice, and extracted with EtOAc. The

organic portion was washed with brine, condensed, and purified by flash column chromatography (0 to 10% of EtOAc in hexanes). The titled compound was obtained as a yellow oil. MS (ES⁺): 206.9 (M+H)⁺. Calc'd for C₁₁H₁₄N₂O₂ - 206.24.

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Preparation CLXXVIII - 1-Ethyl-4,4-dimethyl-7-nitro-1,2,3,4-tetrahydroquinoline:

The mixture of 4,4-dimethyl-7-nitro-1,2,3,4-tetrahydroquinoline (0.48g, 2.33 mmol), iodoethane (0.21 mL, 2.56 mmol), and NaH (60%, 0.10g, 2.5 mmol) in 10 mL of DMF was stirred at RT overnight, and partitioned between EtOAc and H₂O. The combined organic portions were washed with brine, dried with MgSO₄, filtered, and condensed. The crude compound was purified by flash column chromatography (5 to 10% of CH₂Cl₂ in hexanes). The titled compound was obtained as a yellow oil. MS (ES⁺): 235.3 (M+H)⁺. Calc'd for C₁₃H₁₈N₂O₂ - 234.29.

Preparation CLXXIX: 1-Ethyl-4,4-dimethyl-1,2,3,4-tetrahydroquinolin-7-ylamine:

The mixture of 1-ethyl-4,4-dimethyl-7-nitro-1,2,3,4-tetrahydroquinoline (0.28 g) and Pd/C (0.060 g, 10% wt) in 10 mL of EtOAc was placed under H₂ which was provided by a balloon and stirred at RT overnight. Then the mixture was filtered through Celite®, condensed, and the residue was purified by flash column chromatography (2% of EtOAc in CH₂Cl₂). The titled compound was obtained as a pink oil. MS(ES⁺): 204.8 (M+H)⁺. Calc'd for C₁₁H₁₆N - 204.31.

Preparation CLXXX - 1-(4-Nitro-phenyl)-cyclopropanecarbonitrile:

NaOH (5.0 N, 80 mL) was added to a mixture of 4-nitrophenylacetonitrile (10.0 g, 61.7 mmol), 1,2-dibromoethane (8.0 mL, 92.5 mmol), and tetraethylammonium

chloride hydrate (10.2 g, 61.7 mmol) in 200 mL of CH₂Cl₂ at RT. The resulting mixture was stirred at RT for 24 h, diluted with CH₂Cl₂, and acidified with HCl (10%, aq). The organic layer was separated, washed with brine, condensed, and the crude was purified by flash column chromatography. The titled compound was obtained as a light yellowish solid.

Preparation CLXXXI - C-[1-(4-Nitro-phenyl)-cyclopropyl]-methylamine:

The mixture of 1-(4-nitro-phenyl)-cyclopropanecarbonitrile (3.0 g, 15.9 mmol) and borane THF complex (1.0 M solution in THF, 32 mL, 32 mmol) in 50 mL of anhydrous THF was heated at reflux overnight. The mixture was cooled to RT, quenched with 2.5 mL of 50% AcOH aqueous solution, then partitioned between EtOAc and NaHCO₃ (aq). The combined organic portions were washed with brine, dried with MgSO₄, filtered, and condensed. The crude was purified by flash column chromatography (1 to 2% of MeOH in CH₂Cl₂). The titled compound was obtained as a light brownish solid. MS (ES⁺): 192.9. Calc'd for C₁₀H₁₂N₂O₂- 192.2.

Preparation CLXXXII - 2,2,2-Trifluoro-N-[1-(4-nitro-phenyl)-cyclopropylmethyl]-acetamide:

Trifluoroacetic anhydride (5.26 mL, 36.9 mmol) was added to a mixture of C-[1-(4-nitro-phenyl)-cyclopropyl]-methylamine (2.37 g, 12.3 mmol) and triethyl amine (8.6 mL, 61.5 mmol) in 50 mL of CH₂Cl₂ at RT. The resulting mixture was stirred for 2 h. The volatiles were removed under reduced pressure and the residue was partitioned between EtOAc and aqueous NaHCO₃. The organic layer was washed with brine, dried with MgSO₄, filtered, and condensed. The crude compound was purified by flash column chromatography (10 to 20% of EtOAc in hexanes), and the titled compound was obtained as an off-white solid.

Preparation CLXXXIII - 1-(7-Nitro-4-spiro-1'-cyclopropane-3,4-dihydro-1H-isoquinolin-2-yl)-2,2,2-trifluoroethanone:

A mixture of 2,2,2-trifluoro-N-1-(4-nitro-phenyl)-cyclopropylmethyl]-acetamide (3.10 g, 10.7 mmol) and paraformaldehyde (0.54 g, 17.2 mmol) was added to a mixture of 12 mL of glacial AcOH and 20 mL of H₂SO₄ at RT. The resulting mixture was stirred at 40 °C for 12 h, poured into ice-water and extracted with EtOAc. The combined organic portion was washed with NaHCO₃ (aq), H₂O, brine, then dried with MgSO₄, and condensed. The crude compound was purified by flash column chromatography (10 to 20% of EtOAc in hexanes), and the titled compound was obtained as a white solid.

Preparation CLXXXIV - 7-Nitro-4-spiro-1'-cyclopropane-1,2,3,4-tetrahydroisoquinoline:

A mixture of 1-(7-nitro-4-spiro-1'-cyclopropane-3,4-dihydro-1H-isoquinolin-2-yl)-2,2,2-trifluoroethanone (0.32 g, 1.07 mmol) and K₂CO₃ (1.50 g, 14.2 mmol) in 7 mL of MeOH and 2 mL of H₂O was stirred at RT overnight. The mixture was filtered, and the filtrate was concentrated. The residue was dissolved in EtOAc, washed with NH₄Cl (aq), brine, dried with MgSO₄, filtered, and condensed to give the titled compound as a light yellowish solid. MS (ES⁺): 204.9 (M+H)⁺. Calc'd for C₁₁H₁₂N₂O₂ - 204.23.

Preparation CLXXXV - tert-Butyl N-[7-nitro-4-spiro-1'-cyclopropane-3,4-dihydro-1H-isoquinoline-2-carbamate:

The mixture of 7-nitro-4-spiro-1'-cyclopropane-1,2,3,4-tetrahydroisoquinoline (0.20 g, 0.98 mmol), BOC₂O (0.24 g, 1.08 mmol), DMAP (0.025 g, 0.20 mmol), DIEA (0.51 mL, 2.94 mmol) in 10 mL of CH₂Cl₂ was stirred at RT for 2 h. The solvent was removed, the residue was purified by flash

column chromatography (5 to 10% of EtOAc in hexanes), and the titled compound was obtained as a white solid.

Preparation CLXXXVI: *tert*-Butyl N-[7-amino-4-spiro-1'-cyclopropane-3,4-dihydro-1*H*-isoquinoline]carbamate

5 A mixture of *tert*-butyl N-[7-nitro-4-spiro-1'-cyclopropane-3,4-dihydro-2*H*-isoquinoline-2-carbamate (0.27 g, 0.89 mmol) and Pd/C (0.05 g, 10% wt) in 15 mL of MeOH was placed under H₂ which was provided by a balloon and stirred at RT for 1.5
10 h. The mixture was filtered through Celite®, and condensed to give the titled compound as a white solid. MS (ES⁺): 274.8 (M+H)⁺. Calc'd for C₁₆H₂₂N₂O₂ - 274.36.

Preparation CLXXXVII - 4- methyl-6-[2-(1-methyl-ppyrrolidin-2-yl)-ethyl]-pyrimidin -2-ylamine:

15 To a solution of (S)-(-)-1-methyl-2-pyrrolidine (320 mg, 2.78 mmol) in dry THF (10 mL) at 0 °C was added NaH (167 mg, 4.16 mmol). After stirred at RT for 1 h, 2-amino-4-chloro-6-methylpyrimidine (600 mg, 4.16 mmol) in dry THF (10 mL)
20 was added dropwise via the addition funnel. The resulting mixture was heated to reflux under Ar gas for 20 h. The reaction was cooled to RT and quenched with sat. NH₄Cl. Solvent was removed. The residue was partitioned between H₂O and CHCl₃. The organic layer was washed with H₂O, brine,
25 dried over MgSO₄, and evaporated to dryness. This crude compound was purified in column eluted with CH₂Cl₂:MeOH = 95%:5% to yield the title compound. MS *m/z*: 223.2 (M+H). Calc'd. for C₁₂H₂₀N₄ - 222.2.

Preparation CLXXXVIII - (6-bromo-pyridin-2-yl)3-Methyl-but-2-enoic -amide:

30 To a solution of 2-amino-6-bromopyridine (4, 3.015 g, 0.017 mole) and Et₃N (2.40 mL, 0.017 mole) in CH₂Cl₂ (20.0 mL), was added 3,3-dimethylacryloylchloride (1.96 mL, 0.017 mole)

under N₂ at 0 °C. The reaction mixture was slowly warmed to RT and stirred for 12 h. The reaction was quenched by the addition of H₂O (20.0 mL). The organic layer was separated, dried over Na₂SO₄ and evaporated to dryness to yield crude compound which was used without purification.

Preparation CLXXXIX - (6-amino-pyridin-2-yl) 3-Methyl-but-2-enoic-amide:

To a solution of 2-amino-6-bromopyridine (4.30 g, 0.017 mole) and copper (0.214 g, 3.372 mmol) in IPOH (20.0 mL), was added NH₄OH (20.0 mL) in a sealed vessel under N₂. The reaction was sealed and heated to 90 °C for 12 h. The mixture was cooled to RT and EtOAc (50.0 mL) was added. The organic layer was separated, and the aq layer was washed with EtOAc (50.0 mL). The combined organic layers were evaporated to dryness, the resulting residue was dissolved in CH₂Cl₂ (50.0 mL) and washed with H₂O (4 x 30 mL). The organic layer was dried over Na₂SO₄ and evaporated to dryness to yield crude compound which was used without purification.

Preparation CXC - 7-Amino-4,4-dimethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one:

To a mixture of aminopyridine 6 (1.12 g, 5.833 mmol) and AlCl₃ (3.11 g, 0.023 mole) was added chlorobenzene (10.0 mL) in a sealed vessel under Ar. The reaction was sealed and heated to 120 °C for 12 h. The reaction mixture was cooled to RT and the mixture was poured over ice/HCl mixture and extracted with EtOAc (3 x 50.0 mL). The Aq layer was neutralized with solid NaHCO₃ and extracted with EtOAc (5 x 50 mL). The combined organic layers were dried over Na₂SO₄ and evaporated to dryness to yield crude compound which was purified by chromatography (Silica gel, CH₂Cl₂:MeOH, 99:1) yielding the title compound.

Preparation CXCI - 2-[1-(3-Amino-phenyl)-2,2,2-trifluoro-1-trifluoromethyl-ethoxymethyl]-pyrrolidine-1-carboxylic acid tert-butyl ester:

To a mixture of 2-(3-amino-phenyl)-1,1,1,3,3,3-hexafluoro-propan-2-ol (1.30 g), 2-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (1.04 g), PPh₃ (2.64 g) and molecular sieves 4 Å in THF (100 mL) was added DEAD (1.55 mL) slowly. The reaction was stirred at RT for 4 h and at reflux overnight. After filtration to remove solids, the filtrate was concentrated and the residue was taken up into Et₂O. The organic phase was washed with saturated NaHCO₃ and brine. The organic layer was dried over MgSO₄ and evaporated to give a very viscous brown oil, which was purified by chromatography through silica gel (500 g, 30% to 50% EtOAc in hexanes) to afford 2-[1-(3-amino-phenyl)-2,2,2-trifluoro-1-trifluoromethyl-ethoxymethyl]-pyrrolidine-1-carboxylic acid tert-butyl ester as a light brown oil.

Preparation CXCII - N-(3-Amino-5-chloro-phenyl)-2-dimethylamino-acetamide:

To a solution of 5-chloro-benzene-1,3-diamine (3 g, 21 mmol) and dimethylamino-AcOH (2.2 g, 21 mmol) in CH₂Cl₂ (300 mL) was added EDC (5 g, 25 mmol), HOBT (2.9 g, 21 mmol), and DIEA (5 mL). The reaction mixture was stirred at RT overnight. Solvent was removed *in vacuo* and the residue was purified through flash chromatography on silica gel (0-8% MeOH in EtOAc) to give the desired compound.

General Procedure for the preparation of 2,6-diamonipyridines:

To a solution of 2-amino-6-bromopyridine (1.070 g, 6.061 mmol) in 2,4-dimethylphenol (2.0 mL) was added amine (6.667 mmol) and the reaction mixture was heated to 150 °C for 12 h. The mixture was cooled to RT and aq. HCl (2.0 M, 30 mL)

was added. EtOAc (50 mL) was added and the organic layer was separated. The Aq layer was washed with EtOAc (2 x 40 mL) and the combined organic layers were washed with H₂O (50 mL), dried over Na₂SO₄, concentrated under vacuo to yield
5 crude compound which was used without purification.

The following compounds were prepared similarly to the procedure outlined above:

- 10 a) 3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-6'-ylamine:
b) 6-(4-Methyl-piperazin-1-yl)-pyridin-2-ylamine:

Preparation CXCI - 2-Methyl-2-(4-nitrophenyl)propionic acid:

- 15 To a solution of 2-(4-nitrophenyl)propionic acid (50 g, 0.26 mol) in 250 mL of MeOH was added 6 mL of concentrated HCl. The resulting solution was heated at reflux for 16 h. The reaction was diluted with 200 mL of aq. NaHCO₃ and 500 mL of EtOAc. The organic layer was separated, dried over Na₂SO₄,
20 and concentrated. The residue was diluted with 100 mL of THF and added to a suspension of NaH (11.2 g, 0.28 mole, 60 % in mineral oil) in 600 mL of THF. To the resulting mixture was added CH₃I (18.3 mL, 0.29 mole) in one portion. The resulting mixture was stirred for 48 h at 40 °C and diluted
25 with aq. NH₄Cl solution and EtOAc. The organic layer was separated, dried over Na₂SO₄, and concentrated. The residue was used without further purification.

- To a solution of the residue (54 g, 0.24 mole) in 500 mL of MeOH was added 5 N aq. NaOH solution (144 mL, 0.72
30 mole). The mixture was stirred for 16 h at 40 °C, then, concentrated, and the residue was diluted with H₂O (500 mL). The aq. solution was acidified with 2 N HCl to give a precipitate which was filtered and dried to give the titled

compound as a yellowish solid. MS: (ES+) 210 (M+H). Calc'd for $C_{10}H_{12}NO_4$ - 210.20.

Preparation CXCIIV - 2-Methyl-5-[1-methyl-1-(4-nitro-phenyl)-ethyl]-[1,3,4]oxadiazole:

A mixture of 2-methyl-2-(4-nitro-phenyl)-propionic acid (5 g, 24 mmol) and a few drops DMF in $SOCl_2$ was stirred at reflux for 16 h. The resulting solution was concentrated to give corresponding acid chloride as a brown solid.

To a mixture of the acid chloride (2.33 g, 10.2 mmol), acetic acid hydrazide (0.91 g, 12.2 mmol), Et_3N (2.86 mL, 20.2 mmol) in CH_2Cl_2 (50 mL) was added 2 crystals of DMAP at RT. The resulting mixture was stirred for 16 h and concentrated. A solution of the residue in 50 mL of $POCl_3$ was heated at 95 °C for 16 h. The resulting mixture was concentrated and diluted with ice- H_2O and EtOAc. The organic layer was washed with saturated aq. $NaHCO_3$ solution twice, dried over Na_2SO_4 , and concentrated. The residue was purified by SiO_2 chromatography (hexane: EtOAc=1:1) to give the titled compound as a pale yellow crystalline solid. MS: (ES+) 248 (M+H). Calc'd for $C_{12}H_{14}N_3O_3$ - 248.10.

Preparation CXCV - 2-Methyl-5-[1-methyl-1-(4-amino-phenyl)-ethyl]-[1,3,4]oxadiazole:

A mixture of 2-methyl-5-[1-methyl-1-(4-nitro-phenyl)-ethyl]-[1,3,4]oxadiazole (1.36 g, 5.5 mmol) and Pd/C (68 mg) in EtOAc (50 mL) was stirred under 1 atm of H_2 for 16 h. The resulting slurry was filtered over Celite®, and the filtrate was concentrated to give the titled compound as a pale yellow crystalline solid. MS: (ES+) 218 (M+H). Calc'd for $C_{12}H_{16}N_3O$ - 218.12.

Preparation CXCVI - 4-[1-Methyl-1-(4-nitro-phenyl)-ethyl]-pyrimidine:

To a mixture of 1-(4-nitro-phenyl)-propan-2-one (5.32 g, 29.7 mmol), triethylbenzylammonium chloride (0.34 g, 1.5 mmol), and 13 mL of aq. 5N KOH solution (65.3 mmol) in CH₂Cl₂ was added CH₃I (4.06 mL, 65.3 mmol). The resulting mixture was stirred at 40 °C then diluted with EtOAc and H₂O. The organic layer was dried and concentrated.

To the residue (1.0 g, 4.8 mmol) in toluene (30 mL) was added dimethylformamide dimethylacetal (1.27 mL, 9.6 mmol). The resulting mixture was heated at reflux for 6 h, then concentrated to give 1-dimethylamino-4-methyl-4-(4-nitro-phenyl)-pent-1-en-3-one as a yellow solid. MS: (ES+) 263 (M+H). Calc'd for C₁₄H₁₉N₂O₃-263.13.

A mixture of 1-dimethylamino-4-methyl-4-(4-nitro-phenyl)-pent-1-en-3-one (0.5 g, 1.9 mmol), formamidine hydrochloride (0.305 g, 3.8 mmol), and NaOEt (1.29 g, 4.0 mmol) was heated in Smith synthesizer under microwave for 10 min at 150 °C. The resultant was diluted with H₂O and EtOAc. The organic layer was dried, and the residue was used without further purification. MS: (ES+) 244 (M+H). Calc'd for C₁₃H₁₄N₃O₂ - 244.10.

Preparation CXCVII - 5-[1-Methyl-1-(4-nitro-phenyl)-ethyl]-1H-pyrazole:

A mixture of 1-dimethylamino-4-methyl-4-(4-nitro-phenyl)-pent-1-en-3-one (0.36 g, 1.4 mmol) and hydrazine hydrate (1.0 g, 6.25 mmol) in EtOH was heated at 50 °C for 3h. The mixture was concentrated, and the residue was diluted with H₂O and EtOAc. The organic layer was dried over Na₂SO₄ and concentrated to give the titled compound as a yellow solid. MS: (ES+) 232 (M+H.) Calc'd for C₁₂H₁₄N₃O₂ -232.10.

Preparation CXCVIII - 2-Methyl-2-(4-nitro-phenyl)-1-pyrrolidin-yl-propan-1-one:

To a round bottom flask charged with 2-methyl-2-(4-nitro-phenyl)-propionic acid, was added 6.5 mL of SOCl_2 . The
5 mixture was heated to 80 °C, with stirring under inert atmosphere for 3.5 h. The mixture was cooled to RT, and then dried *in vacuo*. The residue was placed under high vacuum. After completely dry, the residue was used without further purification.

10 To the residue was added 10 mL of CH_2Cl_2 , along with Et_3N and the mixture was cooled to 0 °C on an ice/ H_2O bath. Pyrrolidine .46 mL (1.25 eq.) was added into the mixture, then stirred to RT under inert atmosphere. After 3 h of stirring, the mixture was quenched with H_2O , diluted with
15 CH_2Cl_2 , and transferred to a separatory funnel. The organics were collected, combined, dried over Na_2SO_4 and filtered. The crude was concentrated *in vacuo*. After drying, the title compound was produced as an amorphous solid. MS: 263 (M+1); calc'd for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_3$ - 262

20

Preparation CXCIX - 4-(1,1-Dimethyl-2-pyrrolidin-1-yl-ethyl)-phenylamine:

To a 3-neck round bottom flask, charged with 2-Methyl-2-(4-nitro-phenyl)-1-pyrrolidin-yl-propan-1-one was added 66 mL
25 of 1M BH_3/THF soln, while the mixture was maintained at 0 °C on an ice/ H_2O bath. The mixture was stirred under inert atmosphere overnight. A couple drops of 5 N NaOH was added slowly to the reaction mixture for quenching. After stirring an additional 5 min, 22 mL of 5 N NaOH was added
30 into the reaction mixture, then stirred vigorously for 3 h. The mixture was diluted with 50 mL of 1N NaOH and 100 mL of EtOAc, then transferred into a sep. funnel. The organics were collected and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 , then NaHCO_3 soln. was added into the

mixture the organic extracts were dried over Na_2SO_4 , filtered, then concentrated *in vacuo*.

To a round bottom flask charged with Pd/C in MeOH under inert atmosphere, was added 1-[2-methyl-2-(4-nitro-phenyl)-propyl]-pyrrolidine in MeOH and H_2 was added while stirring vigorously overnight. The mixture was filtered through Celite® and concentrated *in vacuo* to yield a light yellow oil. MS: 219 (M+1); calc'd for $\text{C}_{14}\text{H}_{22}\text{N}_2$.

10 **Preparation CC - 1-methyl-1-(4-nitro-phenyl)-ethylamine:**

To a round bottom flask charged with 2-methyl-2-(4-nitro-phenyl)-propionic acid (10 g; 0.0440 mole), was added SOCl_2 (32 mL). The mixture was heated to reflux, until completion of the reaction. After heating, the residual SOCl_2 was removed by *in vacuo*, then placed the residue on high vac. The crude was used without further purification.

To the residue, was added 20 mL toluene and stirred. Then slowly NaN_3 (7.14 g; 0.1099 mole) was added into the mixture, and stirred vigorously under inert atmosphere for 1.5 h. The mixture was poured into 50 mL H_2O and transferred into a sep. funnel, with 50 mL EtOAc. The organics were collected, dried, filtered, and concentrated *in vacuo*. The residue was dissolved in toluene and heated to 100 °C while stirring vigorously under inert atmosphere for 1 h. The solvent was removed *in vacuo*, 20% HCl aq was added and the mixture stirred vigorously under reflux conditions at 100 °C for 9 h. The mixture was evaporated *in-vacuo* and to the residue was added 50 mL of 5 N NaOH and 80 mL EtOAc, then transferred the mixture to a sep. funnel. The organic layer was collected, dried, filtered, and conc. *in vacuo*. The residue was purified on silica-gel column in a solvent gradient of 80% EtOAc/Hexanes to 10% MeOH/ CH_2Cl_2 yielding a brown solid resulted. MS: 181 (M+1); calc'd for $\text{C}_9\text{H}_{12}\text{N}_2\text{O}_2$ -180.

Preparation CCI - [1-(4-Amino-phenyl)-1-methyl-ethyl]-(2-methylsulfanyl-pyrimidin-4-yl)-amine:

To a Personal Chemistry reaction tube, was added 1-methyl-1-(4-nitro-phenyl)-ethylamine, along with 4-chloro-2-methylsulfanyl-pyrimidine, DIEA (2.0 eq) and t-BuOH (0.6 mL). The tube was heated by microwave to 150 °C for 10 min. After heating, the crude was diluted with CH₂Cl₂ and H₂O, then transferred into a sep. funnel. The organics were collected, dried over Na₂SO₄, then concentrated *in vacuo*. The crude was used without further purification.

To a round bottom flask charged with PtO₂ (12% wt.) in MeOH (5 mL), was added crude nitro-intermediate (.170 g; 0.0006 mole). The mixture was stirred vigorously under H₂ for 2.5 h. The mixture was filtered through Celite® and concentrated *in vacuo*. The desired material was purified by silica-gel chromatography in a solvent gradient of 80% EtOAc/Hexanes to 5% MeOH/CH₂Cl₂. After drying in high vacuum, the title compound resulted as a light yellow amorphous solid.

Preparation CCII - 2-(2,2,2-Trifluoro-ethoxy)-isonicotinonitrile:

To the suspension of NaH (2.78 g, 0.11 mole) in THF 100 mL) 2,2,2-trifluoroethanol (10 g, 0.1 mole) was added slowly. The mixture was stirred at RT till it turned clear. A solution of 2-chloro-isonicotinonitrile (13.8 g, 0.1 mole) in THF (100 mL) was slowly added and stirred at reflux for 3 h. After filtration and concentration, the crude oily compound was purified through column chromatography providing pure compound as an oil.

Preparation CCIII - C-[2-(2,2,2-Trifluoro-ethoxy)-pyridin-4-yl]-methylamine hydrogen chloride:

A mixture of 2-(2,2,2-trifluoro-ethoxy)-isonicotinonitrile (3.90 g, 19.40 mmol), 12 N HCl (8.0 mL) and 10% Pd/C (800 mg) in MeOH (100 mL) was stirred under a balloon of H₂ for 7 h. After filtration, the filtrate was concentrated to give compound as a white solid. MS (ES⁺): 206.9 (M+H)⁺. Calc'd. for C₈H₉F₃N₂O - 206.07.

Preparation CCIV - 2-Bromomethyl-3-nitro-benzoic acid methyl ester:

The mixture of methyl 2-methyl-3-nitro benzoate (5.06 g, 25.9 mmol), NBS (5.54 g, 31.1 mmol), and AIBN (0.43 g, 2.59 mmol) in 100 mL of anhydrous CCl₄ was heated at reflux under N₂ for 22 h, cooled to RT, diluted with EtOAc, and washed with Na₂CO₃ (aq). The organic portion was separated, washed with brine, dried with Na₂SO₄, filtered, and condensed. The crude material was purified by flash column chromatography to yield pure product, which was used without further purification.

Preparation CCV - 4-Nitro-2, 3-dihydro-isoindol-1-one:

NH₃ (2.0 M in MeOH, 50 mL) was slowly added to the solution of 2-bromomethyl-3-nitro-benzoic acid methyl ester (4.46 g, contaminated with a small amount of assumed starting material, 16.3 mmol) in 30 mL of MeOH at RT. The resulting mixture was stirred at RT overnight, to provide the title compound as a white solid. MS (ES⁺): 179.2 (M+H)⁺. Calc'd for C₈H₆N₂O₃ - 178.14.

Preparation CCVI - 4-Amino-2, 3-dihydro-isoindol-1-one:

To the suspension of 4-nitro-2,3-dihydro-isoindol-1-one (2.40 g, 13.5 mmol) in 100 mL of MeOH was added Pd/C (10 wt%, 0.36 g). The mixture was then placed under H₂ from a

balloon, stirred at RT for 24 h, filtered through Celite®, and condensed to give the titled compound as a light greenish solid. MS (ES⁺): 149.1 (M+H)⁺. Calc'd for C₈H₈N₂O - 148.16.

5

Preparation CCVII - Pyridin-4-ylmethyl-carbamic acid tert-butyl ester:

Boc anhydride (23 g, 105 mmol) was carefully added to a solution of pyridin-4-yl-methylamine (11 g, 102 mmol) and DMAP (0.5 g, 4 mmol) in CH₂CL₂ (150 mL). The reaction was extended for 1 hr after the addition. The reaction mixture was concentrated *in vacuo* and the residue was recrystallized in EtOAc to afford an off white crystal as the desired compound.

15

Preparation CCVIII - (1-Oxy-pyridin-4-ylmethyl)-carbamic acid tert-butyl ester:

Pyridin-4-ylmethyl-carbamic acid tert-butyl ester (2.1 g, 10 mmol) was dissolved in a one to one mixture of aqueous MeOH (200 mL) with NaHCO₃ (5 g, 60 mmol) and Oxone® (12.3 g, 20 mmol). The mixture was stirred overnight then concentrated *in vacuo* to remove MeOH. The resulted aqueous mixture was diluted with H₂O (150 mL) and filtered. The filter cake was washed with H₂O and dried to afford a white solid as the desired compound.

25

Preparation CCIX - C-(1-Oxy-pyridin-4-yl)-methylamine:

Oxy-pyridin-4-ylmethyl)-carbamic acid tert-butyl ester (2.1 g, 9.4 mmol) was dissolved in a 4 N HCl in dioxane solution (50 mL) and heated to 50 °C for 2 h. After removing solvent *in vacuo*, a white solid was received as an HCl salt of the desired compound.

30

Preparation CCX - 2-(4-Methoxy-benzylamino)-isonicotinonitrile:

To pyridine (500 mL) were added 2-chloroisonicotinonitrile (22.0 g, 159 mmol), para-methoxybenzylamine (25 g, 114% Meq.), and NaHCO₃ (30 g). The mixture was heated under reflux overnight. After cooling to RT, the mixture was filtered and the filter cake was rinsed with CH₂Cl₂. The combined filtrate was concentrated to dryness in vacuum to form a yellow solid. This solid is then recrystallized in EtOAc to give a light yellow crystalline compound and the mother liquor was concentrated and subjected to EtOAc again (repeating three times) to yield the desired compound.

Preparation CCXI - (4-Aminomethyl-pyridin-2-yl)-(4-methoxy-benzyl)-amine:

2-(4-Methoxy-benzylamino)-isonicotinonitrile (12 g, 50 mmole) was dissolved in a mixed solvent of EtOH (800 mL) Et₃N (200 mL) and suspended with 2 g of Pd/C (10%). After removing air with vacuum, the flask was charged with H₂ with a balloon. The H₂ balloon was refilled every morning and evening. Pd/C was recharged twice (1.3 g each) on days 2 and 3. Reaction was completed on the 4th day and the reaction mixture was filtered through a pad of Celite®. The filter cake was rinsed with MeOH and the combined filtrate was concentrated *in vacuo* to give the desired compound as a light brown solid.

Preparation CCXII - 4-Aminomethyl-pyridin-2-ylamine:

(4-Aminomethyl-pyridin-2-yl)-(4-methoxy-benzyl)-amine (12 g, 50 mmol) was dissolved in TFA (150 mL) and heated to reflux for 1 h. After cooling, the reaction mixture was concentrated in vacuum and the residue was partitioned between HCl (1 N, aq.) and EtOAc. The aqueous layer was washed with EtOAc then hexanes and concentrated to dryness

in vacuum to give an off white solid as a dihydrochloric salt.

Preparation CCXIII - 2-Methylamino-isonicotinonitrile:

- 5 To a solution of 2-chloroisonicotinonitrile (22.0 g, 159 mmole) in pyridine (500 mL) was added methylamine in THF (2 N, 160 mL), and NaHCO₃ (54 g). The mixture was heated to 120 °C in a sealed vessel for 40 h. After cooled to RT, the mixture was filtered and the filter cake was washed with
10 CH₂Cl₂. The combined filtrate was concentrated *in vacuo* to give a yellow solid (21 g) as the desired compound.

Preparation CCXIV - (4-Aminomethyl-pyridin-2-yl)-methylamine:

- 15 A suspension of 2-Methylamino-isonicotinonitrile (5.6 g) and Pd/C (10%, 4 g) in EtOH (150 mL) and TEA (40 mL) was placed in a 500 mL Parr Hydrogenation bottle and hydrogenated under 60 psi of H₂ over night. After filtering through a pad of Celite®, the reaction mixture was concentrated *in vacuo* to
20 give a yellow oil as the desired compound.

Preparation CCXV - 3-Fluoro-pyridine 1-oxide:

- 3-Chloroperoxybenzoic acid (70%, 35.0 g, 142 mmol) was added to the solution of 3-fluoropyridine (6.90 g, 71.1 mmol) in
25 200 mL of CH₂Cl₂, the mixture was stirred at RT overnight, washed with a small amount of saturated NaHCO₃ solution, dried with Na₂SO₄, filtered, condensed, the crude compound was purified by flash column chromatography (1 to 2% of MeOH in CH₂Cl₂), the titled compound was obtained as a light
30 yellowish solid. MS (ES⁺): 114.1 (M+H)⁺. Calc'd for C₅H₄FNO - 113.09.

Preparation CCXVI - 3-Fluoro-pyridine-2-carbonitrile:

The mixture of 3-fluoro-pyridine 1-oxide (0.99 g, 8.75 mmol), trimethylsilyl cyanide (4.80 mL, 35.0 mmol), and triethyl amine (1.84 mL, 13.2 mmol) in 100 mL of CH₃CN was heated at reflux overnight. The solvents were removed, under reduced pressure and the residue was partitioned between EtOAc and saturated NaHCO₃. The organic portion was separated, dried with Na₂SO₄, filtered, condensed, the crude compound as purified by flash column chromatography (10 to 20% of EtOAc in hexanes). The titled compound was obtained as a light yellowish solid. MS (ES⁺): 123.1 (M+H)⁺. Calc'd for C₆H₃FN₂ - 122.10.

Preparation CCXVII - C-(3-Fluoro-pyridin-2-yl)-methylamine:

The mixture of 3-fluoro-pyridine-2-carbonitrile (0.81 g, 6.63 mmol) and Pd/C (0.20 g, 10% wt) in 10 mL of MeOH and 2.7 mL of concentrated HCl was placed under H₂ which was provided by a balloon and stirred at RT for 4 h, filtered through Celite®, condensed, the residue was purified by flash column chromatography, 0.13 g of the titled compound was obtained as a light yellowish oil. MS (ES⁺): 127.1 (M+H)⁺. Calc'd for C₆H₇FN₂ - 126.13.

Preparation CCXVIII: 5-Bromo-pyridine-2-carbonitrile:

The mixture of 2,5-dibromopyridine (4.74 g, 20.0 mmol), zinc cyanide (1.40 g, 12.0 mmol), zinc dust (0.059 g, 0.90 mmol), and Pd(dppf)Cl₂.CH₂Cl₂ (0.36 g, 0.44 mmol) in 25 mL of DMF was heated at reflux for 5 h, cooled to RT, diluted with H₂O, extracted with EtOAc, the organic portion was washed with brine, the solvents were removed, the crude compound was purified by flash column chromatography (5 to 15% of EtOAc in hexanes), the titled compound was obtained as an off-white solid.

Preparation CCXIX - 5-Fluoro-pyridine-2-carbonitrile:

The mixture of 5-bromo-pyridine-2-carbonitrile (0.50 g, 2.73 mmol), and KF (0.48 g, 8.20 mmol) in 10 mL of 1-methyl-2-pyrrolidinone was stirred at 175 °C for 18 h, cooled to RT, diluted with H₂O, extracted with EtOAc, the combined organic portions were washed with H₂O, brine, dried with Na₂SO₄, filtered, condensed, the crude compound was purified by flash column chromatography (5 to 20% of EtOAc in hexanes). The titled compound was obtained as an off-white solid.

10

Preparation CCXX - C-(5-Fluoro-pyridin-2-yl)-methylaniline:

The mixture of 5-fluoro-pyridine-2-carbonitrile (0.16 g, 1.27mmol) and Pd/C (0.030 g, 10% wt) in 15 mL of MeOH and 0.50 mL of concentrated HCl was placed under H₂ which was provided by a balloon and stirred at RT for 4 h, filtered through Celite®, condensed, the residue was purified by flash column chromatography. The titled compound was obtained as a light yellowish solid. MS (ES⁺): 127.2 (free base) (M+H)⁺. Calc'd for C₆H₇FN₂ (free base)- 126.13.

20

Preparation CCXXI - 1H-Pyrrolo[2,3-b]pyridine 7-oxide:

To a suspension of 1H-pyrrolo[2,3-b]pyridine (10.0 g) and NaHCO₃ (45.2 g) in 1:1 MeOH/H₂O (1000 mL) was added Oxone® (106 g) in portions during 40 min period. The mixture was stirred at RT for 5 h. The solid was removed by filtration and the filtrate was concentrated to 200 mL in volume. This aqueous phase was extracted with CH₂Cl₂ (200 mL X 7) to afford 1H-pyrrolo[2,3-b]pyridine 7-oxide.

Preparation CCXXII - 4-chloro-1H-pyrrolo[2,3-b]pyridine:

To a cooled POCl₃ (50 mL) in a dried round bottom flask, 1H-pyrrolo[2,3-b]pyridine 7-oxide (5.73 g, Step A) was added in portions. The mixture was heated to reflux for 5 h. After cooled down to RT, POCl₃ was evaporated under high vacuum

30

under gentle heating (40-50 °C) to obtain black residue. 50 mL of H₂O was added slowly and pH was adjusted to 8-9 with Na₂CO₃ (first with solid, then saturated aqueous solution). The resulting precipitate was collected by filtration,
5 washed with cold H₂O and dried in a vacuum oven (50 °C) to give 4-chloro-1H-pyrrolo[2,3-b]pyridine as tan powder.

Preparation CCXXIII - 1-(4-iodo-pyrrolo[2,3-b]pyridin-1-yl)-ethanone:

10 To a suspension of 4-chloro-1H-pyrrolo[2,3-b]pyridine (3.80 g, step B) and NaI (19.15 g) in CH₃CN (40 mL) was added acetyl chloride (5.0 mL) slowly. The mixture was heated to reflux for overnight. After cooled to RT, 40 mL of 10% Na₂CO₃ and 40 mL of 10% NaHSO₃ were added. After stirring for
15 15 min, the mixture was extracted with EtOAc 4 times. The combined organic phases were washed with brine, dried over MgSO₄ and concentrated to give a brown residue as the crude compound, which was purified by chromatography through silica gel (220 g, 5 to 15% EtOAc/hexanes to afford 1-(4-
20 iodo-pyrrolo[2,3-b]pyridin-1-yl)-ethanone as white solid.

Preparation CCXXIV - 1-acetyl-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile:

A mixture of 1-(4-iodo-pyrrolo[2,3-b]pyridin-1-yl)-ethanone
25 (4.30 g, Step C), CuCN (6.841 g), Pd₂dba₃ (0.729 g), and dppf (1.636 g) in 85 mL of dioxane was heated to reflux for 2 h. Solid was removed by filtration through a pad of Celite®. The filtrate was concentrated to give a yellow solid as crude compound, which was purified by
30 chromatography through silica gel (250 g, 5-30% EtOAc/hexanes, stepwise gradient) to afford 1-acetyl-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile as a white fluffy solid.

Preparation CCXXV - 1-(4-aminomethyl-pyrrolo[2,3-b]pyridin-1-yl)-ethanone:

A mixture of 1-acetyl-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile (0.872 g, step D), 10% Pd/C (0.882 g), 20 mL of Et₃N, and 80 mL of EtOH was stirred at RT under balloon pressure of H₂ for overnight. Solid was removed by filtration through a pad of Celite® and the filtrate was concentrated to yield a cream color residue, which was purified by chromatography through silica gel (70 g, 2 to 5% MeOH/CHCl₃ with 1% NH₄OH) to afford 1-(4-aminomethyl-pyrrolo[2,3-b]pyridin-1-yl)-ethanone as a white solid.

Preparation CCXXVI - N-(1-acetyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-ylmethyl)-acetamide:

To a mixture of 1-acetyl-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile (0.691 g, Example 15, Step D), 10% Pd/C (0.702 g), 5 mL of Et₃N, and 20 mL of EtOAc was added acetic anhydride (1.0 mL). The mixture was stirred at RT under balloon pressure of H₂ for overnight. Solid was removed by filtration through a pad of Celite® and the filtrate was concentrated to yield a white residue, which was purified by chromatography through silica gel (150 g, 1 to 5% MeOH/CHCl₃ with 1% NH₄OH, stepwise gradient) to afford N-(1-acetyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-ylmethyl)-acetamide (0.50 g) as white solid.

Preparation CCXXVII - C-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl)-methylamine hydrogen chloride salt:

A mixture of N-(1-acetyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-ylmethyl)-acetamide (0.50 g, Step A), HCl (conc., 3 mL) and EtOH (12 mL) was heated to 70 °C for overnight. Additional 3 mL of conc. HCl was added to the reaction and the heating was continued for 3 more days. Solvent was evaporated to give a white residue as crude C-

(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl)-methylanine HCl salt, which was used without further purification.

5 **General Procedure for the Preparation of 2-amino-4-methylaminopyridines**

Preparation CCXXVIII - 2-aminoisonicotinonitrile:

To a slurry of 2-chloro-4-cyanopyridine (10.00 g, 0.079 mole) and sodiumbicarbonate (19.92 g, 0.237 mole) in amine
10 (0.174 mole) was added pyridine (35.0 mL) and the reaction was heated to 90 °C for 3 h. The reaction was then cooled to RT, diluted with the addition of CH₂Cl₂ (100 mL) and filtered. The solid was washed with EtOAc. Combined washes were concentrated in vacuo. A mixture of MeOH/hexanes was
15 added and kept in the fridge for 12 h. The crystals that formed were filtered and washed with hexanes.

Preparation CCXXIX - 2-amino-4-methylaminopyridine:

To a mixture of 2-aminoisonicotinonitrile (0.043 mole) and
20 Pd/C (10%, 6.00 g) was added Et₃N (40.0 mL) and EtOH (160.0 mL) in a parr bottle and hydrogenated at 50 psi for 12 h. Crude mixture was filtered through Celite®, concentrated under vacuo and dried under high vacuum to yield compound.

25 **Preparation CCXXX - (2-Pyrrolidin-1-yl-pyridin-4-yl)-methylanine:**

Prepared according to the general procedure with pyrrolidine as the amine.

30 **Preparation CCXXXI - (2-Morpholin-4-yl-pyridin-4-yl)-methylanine:**

Prepared according to the general procedure with morpholine as the amine.

Preparation CCXXXII - 3,9,9-Trimethyl-6-nitro-4,9-dihydro-3H-3-aza-fluorene:

4-[1-(2-Bromo-4-nitro-phenyl)-1-methyl-ethyl]-1-methyl-1,2,3,6-tetrahydro-pyridine (9 g), Pd(OAc)₂ (900 mg), and
5 DIEA (15 mL) was dissolved in DMF (300 mL), and heated to 80°C overnight. Solvents were removed *in vacuo*. The residue was partitioned between CH₂Cl₂/NaHCO₃(sat, aq.). The CH₂Cl₂ layer was washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified via flash
10 chromatography on silica to give the desired compound. (MS: M+H=257)

Preparation CCXXXIII - 3,9,9-Trimethyl-2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluoren-6-ylamine(156):

15 3,9,9-Trimethyl-6-nitro-4,9-dihydro-3H-3-aza-fluorene (700 mg) was dissolved in EtOH (20 mL) with aqueous HCl (1 N, 5 mL) and suspended with Pd/C (10%, 100 mg). The flask was capped with a balloon filled with H₂. The reaction was completed in 6 h at RT. The reaction mixture was filtered
20 through a layer of Celite® with MeOH. The combined filtrate was concentrated to give desired compound. (MS: M+H=231).

Preparation CCXXXIV - 2-Chloro-5-nitro-phenol:

A mixture of 2-chloro-4-nitroanisole (10 g, 53.3 mmol) and
25 pyridinium chloride (50 g, 426 mmol) was heated at 200 °C for 3 h. After cooling to RT, the mixture was dissolved in 150 mL of aqueous 2 N HCl and 150 mL of EtOAc. The organic phase was separated and was washed with aqueous 2 N HCl (2 x 100 mL). The resulting organic phase was dried over MgSO₄
30 and concentrated *in vacuo*. The title compound was obtained via chromatography (silica gel, 10:1 hexane/EtOAc) as a yellow solid.

Preparation CCXXXV - 3-(2-Chloro-5-nitro-phenoxyethyl)-azetidine-1-carboxylic acid tert-butyl ester:

To the mixture of 2-chloro-5-nitro-phenol (1.31 g, 7.54 mmol) and K_2CO_3 (1.57 g, 11.31 mmol) in 20 mL of DMF was
5 added 3-methanesulfonyloxymethyl-azetidine-1-carboxylic acid tert-butyl ester (2.0 g, 7.54 mol). The reaction mixture was stirred at 50 °C for 1 h. After cooling to room temperature, the reaction mixture was diluted in 100 mL of EtOAc and quenched with 50 mL of water. The organic layer was
10 separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuum. The title compound was obtained via column chromatography (silica gel, 1;1 hexane/EtOAc) as yellow oil with 93% yield.

15

Preparation CCXXXVI - 3-(5-Amino-2-chloro-phenoxyethyl)-azetidine-1-carboxylic acid tert-butyl ester:

To a solution of 3-(2-chloro-5-nitro-phenoxyethyl)-azetidine-1-carboxylic acid tert-butyl ester (2.5 g, 7.29
20 mmol) in 60 mL of MeOH/ H_2O (1:1) and 3 mL of acetic acid (J.T. Baker) was added Zn powder (2.3 g, 36.47 mmol, Aldrich) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h then stirred at 10 °C for 2 h. The resulting mixture was filtered through a Celite® pad and the filtrate was
25 concentrated *in vacuo*. The residue was treated with 60 mL of saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine and dried with $MgSO_4$. The resulting solution was concentrated *in vacuo* and the title compound was obtained by column
30 chromatography (silica gel, EtOAc) as a yellow solid.

Preparation CCXXXVII: 3-(Benzotriazol-1-yloxy)-6-chloro-pyridazine-4-carboxylic acid (4-tert-butyl-phenyl)-amide:

A mixture of 3,6-dichloropyridazine-4-carboxylic acid (1.00 g, 5.18 mmol), 4-tert-butylaniline (0.92 mL, 5.60 mmol),
5 TBTU (1.75 g, 5.44 mmol), and DIEA (1.80 mL, 10.4 mmol) in 7.5 mL of anhydrous DMF was stirred at RT under N₂ overnight. The mixture was diluted with H₂O, extracted with EtOAc, and the combined organic portions were washed with brine, dried with Na₂SO₄, filtered, and condensed. The
10 crude compound was purified by flash column chromatography (hexanes/EtOAc/CH₂Cl₂, 9:0:1 to 7:2:1), to provide the desired compound as a light yellowish solid. MS (ES⁺): 423.0 (M+H)⁺. Calc'd for C₂₁H₁₉ClN₆O₂ - 422.87.

15 **Preparation CCXXXVIII - 3-Hydroxymethyl-azetidine-1-carboxylic acid benzyl ester:**

To a mixture of azetidine-1,3-dicarboxylic acid monobenzyl ester (6.4 g) in THF (200 mL) was added BH₃•THF (6 eq, 163 mL, 1 M solution) dropwise via an addition funnel at -40 °C
20 under an N₂ atmosphere. The solution was warmed to RT and stirred overnight. To the reaction, 5 N NaOH (50 mL) was added and then concentrated under vacuum. The resulting aqueous solution was extracted with Et₂O (3 x 100 mL). The organic layer was dried over Na₂SO₄ and evaporated to give
25 the title compound which was used without further purification.

Preparation CCXXXIX - 3-Methanesulfonyloxymethyl-azetidine-1-carboxylic acid benzyl ester:

30 3-Hydroxymethyl-azetidine-1,3-dicarboxylic acid monobenzyl ester (6.6 g) was dissolved in CH₂Cl₂ (100 mL) and brought to -15 °C. While stirring, TEA was added (3 eq, 9.43 g) followed by methanesulphonic chloride (2.0 eq, 7.69 g) and allowed to come to RT and stirred for 1 h. The resulting

organic solution was extracted with water (3 x 100 mL). The organic layer was dried over Na_2SO_4 and evaporated to give the desired product as a clear oil which was used without further purification.

5

Preparation CCXL - 3-Nitro-5-trifluoromethyl-phenol:

A flask containing 1-Methoxy-3-nitro-5-trifluoromethyl-benzene (10g) and hydrochloride pyridine (10 eq, 52.0 g) was heated to 210 C and stirred for 12 h. Once complete, the
10 reaction was cooled and the residue was dissolved in CH_2Cl_2 and washed twice with water (100 mL). The organic layer was concentrated under vacuum and then set in the freezer overnight. The resulting crystalline product was filtered off and washed with ether and used as is.

15

Preparation CCXLI - 3-(3-Nitro-5-trifluoromethyl-phenoxy-methyl)-azetidine-1-carboxylic acid benzyl ester:

A mixture of 3-nitro-5-trifluoromethyl-phenol (750 mg, Step C), K_2CO_3 (3 eq., 1.5 g) and 3-hydroxymethyl-azetidine-1-carboxylic acid benzyl ester (1.1 eq., 1.2 g) in DMF was
20 heated to 80 C for 1 h. The solution was cooled to RT then filtered and concentrated under vacuum. The residue was dissolved in CH_2Cl_2 and washed with H_2O twice, followed by brine. The organic layer was dried over Na_2SO_4 and
25 evaporated under reduced pressure. The residue was purified by column chromatography using 5% MeOH/ CH_2Cl_2 to provide the desired compound as a colorless solid.

Preparation CCXLII - 3-(3-amino-5-trifluoromethyl-phenoxy-methyl)-azetidine-1-carboxylic acid benzyl ester:

30 To a solution of 3-(3-nitro-5-trifluoromethyl-mg) and NH_4Cl (1.1 eq., 80 mg) was added iron dust (3 eq., 220 mg) in a 10% water/EtOH solution. The solution was heated to reflux for 6 h. The solution was cooled, then filtered through a

pad of Celite®. The resulting solution was concentrated under vacuum to provide the desired compound as a dark yellow solid and used as is.

5

Preparation CCXLIII - 3-nitro-5-(trifluoromethyl)phenylamine

To a solution of 3,5-dinitrobenzotrifluoride (10 g, 42 mmol, 1 eq.) in 150 mL of EtOH was added 17.6 mL (258.3 mmol, 6.15 eq.) of ammonium sulfide in water (50% by weight, Aldrich). The reaction was heated to reflux for 16 h during which time it became orange and a yellow precipitate formed. After cooling the volume was reduced to approximately 50 mL. The solid was removed by filtration and the filtrate evaporated to dryness *in vacuo*. The resulting orange solid was purified by column chromatography eluting with a step gradient of 20-30% EtOAc:hexane to provide the compound as a yellow/orange solid.

Preparation CCXLIV - N-(3-nitro-5-(trifluoromethyl)phenyl) methanesulfonamide

3-Nitro-5-(trifluoromethyl)phenylamine (2 g, 9.7 mmol, 1 eq) was dissolved in 100 mL of CH₂Cl₂. The yellow solution was cooled to 0 °C. Et₃N (2 mL, 14.55 mmol, 1.5 eq) was added followed by mesyl chloride (0.75 mL, 9.7 mmol, 1 eq). The reaction was stirred for 2 h at 0 °C and warmed to RT. Pyridine (0.785 mL, 9.7 mmol, 1 eq) and a catalytic amount of dimethylamine pyridine were added. The reaction was stirred at RT for 16 h. An additional equivalent of mesyl chloride was added and the reaction was heated to reflux for 24 h. After cooling, the solvent was removed *in vacuo*, and the residue redissolved in CH₂Cl₂. The solution was washed twice with 2 N HCl and once with brine. After drying over Na₂SO₄, the solution was filtered and the solvent removed. The resulting solid was triturated briefly

with 10% EtOAc:hexane to provide a white solid that was a mixture of sulfonimide and sulfonimide.

The above mixture was dissolved in 20 mL of MeOH that had been saturated with K_2CO_3 . After 30 min the reaction
5 was stripped and the resulting solid portioned between 2 N HCl and CH_2Cl_2 . The CH_2Cl_2 was dried over Na_2SO_4 and stripped to provide an off-white solid.

10 **Preparation CCXLV - (3S)-tetrahydro-3-furanyl 3-nitro-5-(trifluoromethyl)phenylcarbamate**

3-(S)-Hydroxytetrahydrofuran (4.8 mL, 60.7 mmol, 5 eq) was dissolved in 60 mL of toluene. The solution was cooled to 0 °C and Et_3N (5.1 mL, 36.4 mmol, 3 eq) was added. Trichloromethyl chloroformate (3.65 mL, 30.33 mmol, 2.5 eq)
15 was added slowly. The solution was stirred at 0 °C for 45 min. 3-Amino-5-nitrobenzotrifluoride (2.5 g, 12.13 mmol, 1 eq) was added dropwise in 20 mL of toluene. The reaction was stirred at 0 °C for 1 h. An additional 5 eq of 3-(S)-hydroxytetrahydrofuran was converted to the chloroformate as
20 described above, and added to the reaction mixture. After an additional h at 0 °C, the reaction was heated to 60 °C for 1 h. The reaction was cooled to RT and concentrated. The residue was dissolved in EtOAc, washed twice with saturated NH_4Cl and once with brine. After being dried over
25 Na_2SO_4 the solution was filtered and the solvent removed *in vacuo*. The crude product was purified using a Biotage chromatography system eluting with a gradient of 5% to 35% EtOAc:hexane to yield the desired compound.

30 **Preparation CCXLVI - N-(2-((3-nitro-5-(trifluoromethyl)phenyl)oxy)ethyl)-methanesulfonamide**

2-((3-Nitro-5-(trifluoromethyl)phenyl)oxy)ethylamine (4.05 g, 16.2 mmol, 1 eq) was dissolved in 100 mL of CH_2Cl_2 . The solution was cooled to 0 °C. Pyridine (2.6 mL, 32.4

mmol, 2 eq) was added followed by mesyl chloride (1.25 mL, 16.2 mmol, 1 eq). The reaction was stirred for 18 h during which time it was warmed slowly to RT. The solvent was removed *in vacuo*, and the residue dissolved in EtOAc. The resulting solution was washed twice with 2 N HCl, once with water, and 3x with brine. After being dried over Na₂SO₄ the solution was filtered and concentrated. The crude was purified by silica gel chromatography eluting with 50% to 60% EtOAc:hexane to yield the desired compound.

Preparation CCXLVII - N-(2-((3-amino-5-(trifluoromethyl)phenyl)oxy)ethyl)methanesulfonamide

N-(2-((3-Nitro-5-(trifluoromethyl)phenyl)oxy)ethyl)-methanesulfonamide (1.7 g, 5.2 mmol, 1 eq) was dissolved in 50 mL of MeOH. 10% Pd/C (170 mg, 10 weight %) was added and the reaction sparged with H₂. The suspension was stirred for 5 h, then filtered through Celite®. The filtrate was stripped to yield the title compound.

The following compounds were prepared similarly to the procedure outlined above:

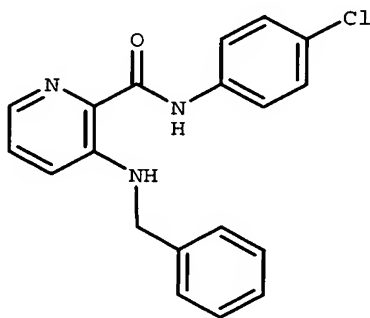
- a) 3-(((2R)-1-acetyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenylamine.
- b) (3S)-tetrahydro-3-furanyl 3-amino-5-(trifluoromethyl)phenylcarbamate.
- c) N-(3-amino-5-(trifluoromethyl)phenyl)-methanesulfonamide

Preparation CCXLVIII - (2R)-1-acetyl-2-((3-nitro-5-(trifluoromethyl)phenyl)oxy)methylpyrrolidine

(2R)-2-((3-nitro-5-(trifluoromethyl)phenyl)oxy)methylpyrrolidine (3.46 g, 11.9 mmol, 1 eq) was dissolved in 100 mL of CH₂Cl₂. Et₃N (5 mL, 35.7 mmol, 3 eq) was added

followed by Ac₂O (1.2 mL, 13.1 mmol, 1.1 eq). The reaction was stirred at RT for 1.5 h. The solvent was removed *in vacuo* and the residue dissolved in EtOAc. The solution was washed once each with saturated NH₄Cl, 1 N HCl, and twice with brine. The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was purified on a Biotage chromatography system eluting with a gradient of 10% to 75% EtOAc:hexane to yield the title compound.

Example 1



N-(4-Chlorophenyl){3-[benzylamino](2-pyridyl)}carboxamide

Step A - Preparation of (3-amino-(2-pyridyl))-N-(4-chlorophenyl)carboxamide

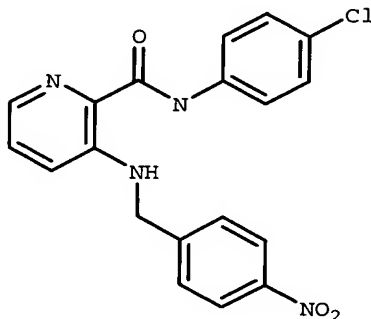
To a mixture of 3-aminopicolinic acid (552 mg, 4.0 mmol, 1.0 eq) and 4-chloroaniline (1.02 g, 8.0 mmol, 2.0 eq) in CH₂Cl₂ was added EDC (1.2 eq), HOBt (0.5 eq) and TEA (1.2 eq). The reaction was stirred at RT overnight, diluted with CH₂Cl₂, washed with NH₄Cl, dried over Na₂SO₄, filtered and concentrated *in vacuo*, purified by flash chromatography (4% MeOH/CH₂Cl₂) to give the amide as a white solid. MS (ES⁺): 248 (M+H)⁺; (ES⁻): 246 (M-H)⁻.

Step B - Preparation of N-(4-chlorophenyl){3-[(4-phenylmethyl)amino](2-pyridyl)}carboxamide

To a mixture of the amide from Step A (1.0 eq.) and 4-benzaldehyde (1.0 eq.) in CH₂Cl₂ was added NaBH(OAc)₃ (1.5 eq). The resulted mixture was stirred for 2 days at RT, diluted with CH₂Cl₂, washed with saturated NH₄Cl solution, dried over Na₂SO₄, filtered and concentrated. The crude material was purified through flash chromatography (4% MeOH/CH₂Cl₂) to give the title compound as a white solid. MS (ES⁺): 338 (M+H)⁺; (ES⁻): 336 (M-H)⁻. Calc'd for C₁₉H₁₆ClN₃O - 337.81.

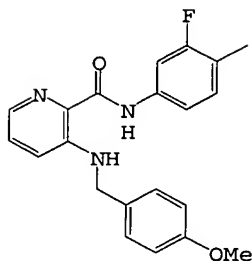
The following compounds (Examples 2-4) were analogously synthesized by the method described in Example 1.

Example 2



N-(4-Chlorophenyl)(3-{[(4-nitrophenyl)methyl]amino}(2-pyridyl))-carboxamide

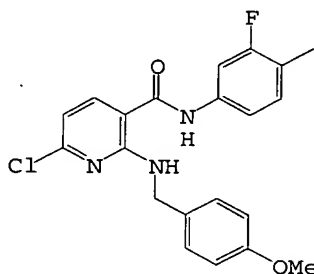
MS (ES⁺): 383 (M+H)⁺; (ES⁻): 381 (M-H)⁻. Calc'd for C₁₉H₁₅ClN₄O₃ - 382.81.

Example 3

5 **(2-[[[(4-methoxyphenyl)methyl]amino](2-pyridyl)]-N-(3-fluoro-4-methylphenyl)carboxamide**

MS (ES⁺): 366 (M+H)⁺. Calc'd for C₂₁H₂₀FN₃O₂ - 365.41.

10

Example 4

15 **(6-chloro-2-[[[(4-methoxyphenyl)methyl]amino](3-pyridyl)]-N-(3-fluoro-4-methylphenyl)carboxamide**

Step A - Preparation of 6-chloro-2-[[[(4-methoxyphenyl)methyl]amino]pyridine-3-carboxylic acid

20 A mixture of 2,6-dichloronicotinic acid (1 g, 5.5 mmol) and 4-methoxybenzylamine (1 mL, 7.7 mmol) in a sealed tube was heated at 150 °C for 3h and 120 °C for 16 h. The resulting solution was cooled to RT and CH₂Cl₂ (10 mL) was added. A precipitate which formed was filtered and washed with CH₂Cl₂ (20 mL). The filtrate was concentrated, dissolved in EtOAc (30 mL), and extracted with NaOH (2 N, 3

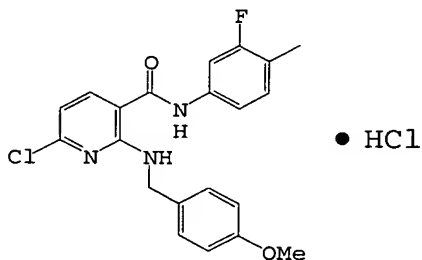
x 15 mL). The combined aqueous solution was acidified with HCl (1 N) to pH 7, and extracted with CH₂Cl₂ (3 x 20 mL). The combined extracts were dried and concentrated. The compound was purified on SiO₂ column (eluted with a solution of hexane-EtOAc 2:1) to give a yellowish solid.

Step B - Preparation of (6-chloro-2-[[(4-methoxyphenyl)methyl]amino] (3-pyridyl))-N-(3-fluoro-4-methylphenyl)carboxamide

A mixture of 6-chloro-2-[[(4-methoxyphenyl)methyl]amino]pyridine-3-carboxylic acid from Step A (100 mg, 0.34 mmol), EDC (107 mg, 0.56 mmol), HOBT (51 mg, 0.37 mmol) and DIEA (0.1 mL) in CH₂Cl₂ (10 mL) was stirred at RT under N₂ atmosphere for 16 h. It was taken up in CH₂Cl₂ and washed with H₂O then aqueous NaHCO₃. The CH₂Cl₂ was evaporated and the oil was placed on a silica gel GF prep plate and eluted with a solution of hexane-EtOAc (4:1). M+H 400.2, M-H 398.1. Calc'd for C₂₁H₁₉ClFN₃O₂: 399.1.

20

Example 5



(6-Chloro-2-[[(4-methoxyphenyl)methyl]amino] (3-pyridyl))-N-(3-fluoro-4-methylphenyl)carboxamide hydrochloride

(6-Chloro-2-[[(4-methoxyphenyl)methyl]amino] (3-pyridyl))-N-(3-fluoro-4-methylphenyl)carboxamide (Example 4) was dissolved in MeOH (0.5 mL) and added to a solution of

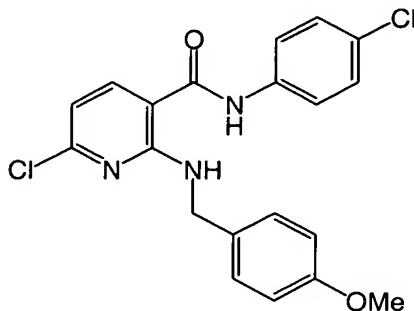
A-735C

- 242 -

HCl-Et₂O. The precipitate was collected and washed with Et₂O to give light yellow solid. MS (ES⁺): 400.2 (M+H); (ES⁻): 398 (M-H). Calc'd for C₂₁H₁₉ClFN₃O₂ - 399.851.

5

Example 6



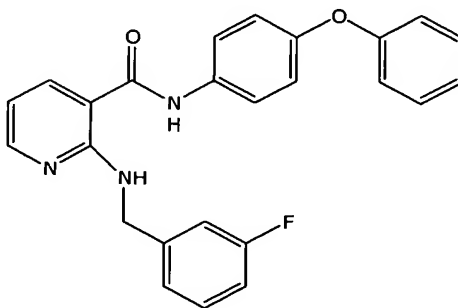
10

(6-Chloro-2-([(4-methoxyphenyl)methyl]amino)(3-pyridyl))-N-(4-chlorophenyl)carboxamide

The title compound was analogously synthesized by method described in Example 4. MS (ES⁺): 403 (M+H); (ES⁻): 401 (M-H). Calc'd for C₂₀H₁₇Cl₂N₃O₂ - 402.28.

15

Example 7



20

2-(3-Fluoro-benzylamino)-N-(4-phenoxy-phenyl)-nicotinamide

Step A: Preparation of 2-chloro-N-(4-phenoxy-phenyl)-nicotinamide

2-Chloropyridine-3-carbonyl chloride (9.15 g, 0.052 mole) was added to a stirred solution of 4-phenoxyaniline (10.00 g, 0.054 mole) and DIEA (10.00 mL, 0.057 mole) in CH₂Cl₂ (100 mL) at RT. The mixture was stirred for 48 h before removal of solvent under reduced pressure. The resulting residue was dissolved in EtOAc and washed several times with saturated NaHCO₃ aqueous solution and brine, respectively. The organic layer was dried over Na₂SO₄ and evaporated to dryness. This material was re-crystallized from EtOAc/Hexane mixtures followed by filtration and rinsing with Et₂O to leave the desired compound as a white solid. MS m/z: 325 (M+1); 323 (M-1)

Step B: 2-(3-Fluoro-benzylamino)-N-(4-phenoxy-phenyl)-nicotinamide

2-Chloro-N-(4-phenoxy-phenyl)-nicotinamide (0.025 g, 0.077 mmol) (Step A) and 3-fluorobenzylamine (0.029 g, 2.31 mmol) were combined and heated at 120 °C neat for 18 h. After cooling to RT, the title compound was obtained through purification via preparative HPLC as the TFA salt. MS: (ES+) 414 (M+1)⁺; (ES-): 412 (M-1)⁻. Calc'd. for C₂₅H₂₀FN₃O₂ - 413.15.

The following compounds (Examples 8-37) were prepared by the method similar to that described in Example 7.

O=C1NC(Cc2ccc(C(F)(F)F)cc2)c3ccncc3N1c4ccc(Oc5ccccc5)cc4

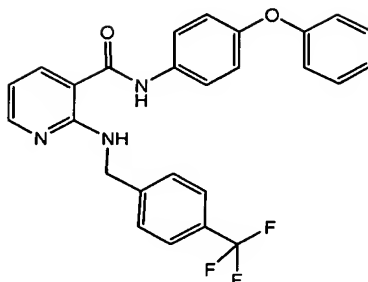
5

10

O=C1C(=Nc2ccc(Oc3ccccc3)cc2)N(Cc4ccc(F)cc4)c5cccnc15

15

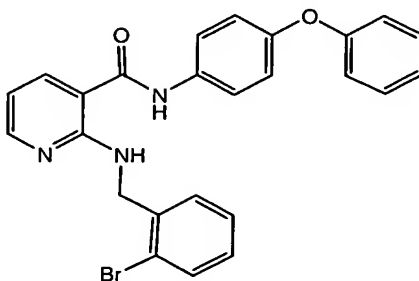
20

Example 10

5 **N-(4-Phenoxy-phenyl)-2-(4-trifluoromethyl-benzylamino)-
nicotinamide**

MS: (ES+) 464 (M+1)⁺; (ES-): 462 (M-1)⁻. Calc'd. for
C₂₆H₂₀F₃N₃O₂ - 463.15.

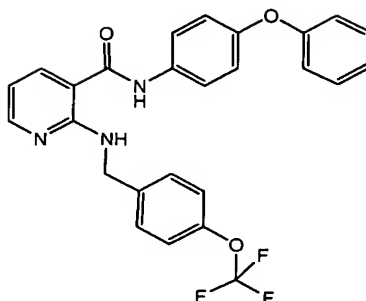
10

Example 11

15 **2-(2-Bromo-benzylamino)-N-(4-phenoxy-phenyl)-nicotinamide**

MS: (ES+) 475 (M+1)⁺; (ES-): 473 (M-1)⁻. Calc'd. for
C₂₅H₂₀BrN₃O₂ - 473.07.

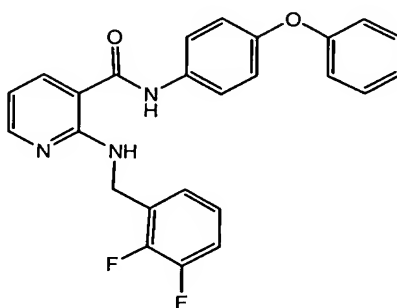
20

Example 12

5 **N-(4-Phenoxy-phenyl)-2-(4-trifluoromethoxy-benzylamino)-
nicotinamide**

MS: (ES+) 480 (M+1)⁺; (ES-): 478 (M-1)⁻. Calc'd. for
C₂₆H₂₀F₃N₃O₃ - 479.15.

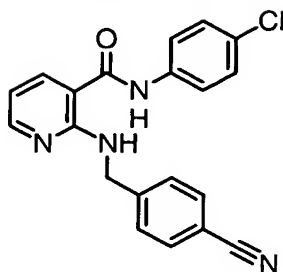
10

Example 13

15 **2-(2,3-Difluorobenzylamino)-N-(4-phenoxyphenyl)-nicotinamide**

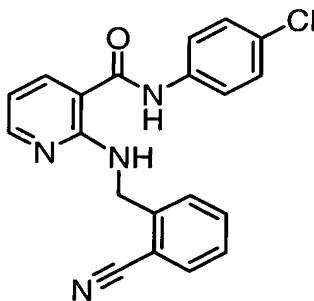
MS: (ES+) 432 (M+1)⁺; (ES-): 430 (M-1)⁻. Calc'd. for
C₂₅H₁₉F₂N₃O₂ - 431.14.

20

Example 14

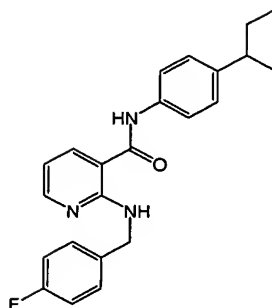
N-(4-Chlorophenyl)-2-([(4-cyanophenyl)methyl]amino)-3-pyridylcarboxamide

MS (ES+): 363 (M+H); (ES-): 361 (M-H). Calc'd. for $C_{20}H_{15}ClN_4O$ - 362.81.

Example 15

N-(4-Chlorophenyl)-2-([(2-cyanophenyl)methyl]amino)-3-pyridylcarboxamide

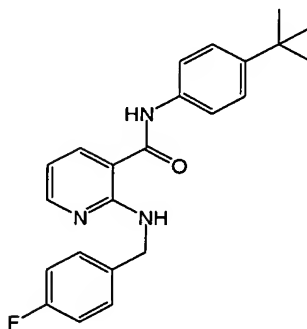
MS (ES+): 363 (M+H); (ES-): 361 (M-H). Calc'd. for $C_{20}H_{15}ClN_4O$ - 362.81.

Example 16

N-(4-sec-butylphenyl)-2-[(4-fluorobenzyl)amino]nicotinamide

5

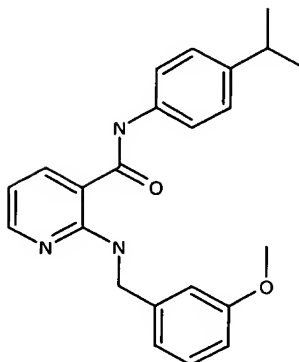
MS: (ES+) 378.2 (M+H); (ES-) 376.2 (M-H). Calc'd for
 $C_{23}H_{24}FN_3O$ - 377.45.

Example 17

10

N-(4-tert-Butylphenyl)-2-[(4-fluorobenzyl)amino]nicotinamide

MS: (ES+) 378.2 (M+H); (ES-) 376. (M-H). Calc'd for
15 $C_{23}H_{24}FN_3O$ - 377.45.

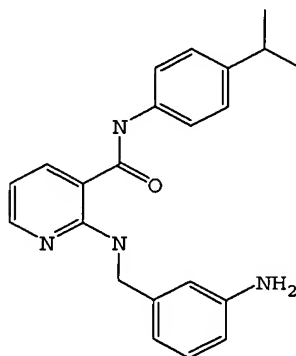
Example 18

**N-(4-Isopropyl-phenyl)-2-(3-methoxy-benzylamino)-
nicotinamide**

5

MS (ES+): 376 (M+H)⁺; (ES-): 374 (M-H)⁻. Calc'd
C₂₃H₂₅N₃O₂ - 375.47.

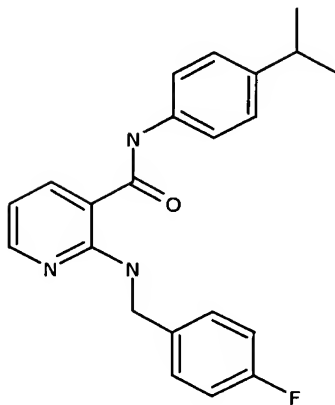
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Example 19

**(2-([(3-Aminophenyl)methyl]amino}(3-pyridyl))-N-[4-
(methylethyl)phenyl]carboxamide**

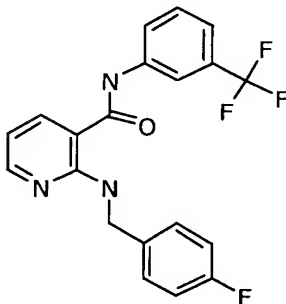
15

MS (ES+): 361 (M+H)⁺; (ES-): 359 (M-H)⁻. Calc'd C₂₂H₂₄N₄O
- 360.46.

Example 20

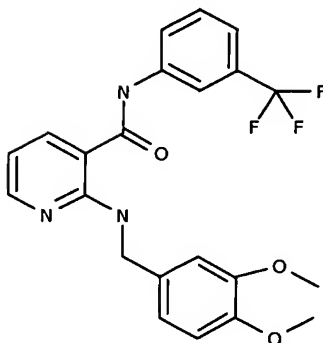
(2-[[4-(4-Fluorophenyl)methyl]amino] (3-pyridyl))-N-[4-(methylethyl)phenyl]carboxamide

MS (ES+): 364 (M+H)⁺; (ES-): 362. Calc'd C₂₂H₂₂FN₃O - 363.43.

Example 21

(2-[[4-(4-Fluorophenyl)methyl]amino] (3-pyridyl))-N-[3-(trifluoromethyl)phenyl]carboxamide

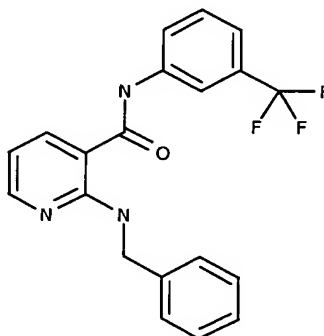
MS: (ES+) 390 (M+H); (ES-) 388. (M-H). Calc'd for C₂₀H₁₅F₄N₃O - 389.35.

Example 22

5 (2-[[3-(trifluoromethyl)phenyl]amino]pyridin-3-yl)-(3,4-dimethoxyphenyl)methylcarbamate

MS: (ES+) 432 (M+H); (ES-) 430. (M-H). Calc'd for
C₂₀H₂₀F₃N₃O₃: 431.41.

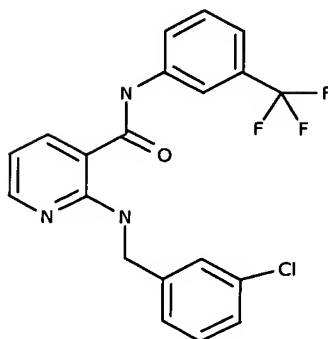
10

Example 23

15

{2-[Benzylamino]pyridin-3-yl)-(3-(trifluoromethyl)phenyl)methylcarbamate

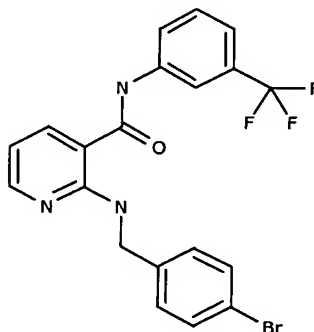
MS: (ES+) 372 (M+H); (ES-) 370. (M-H). Calc'd for
20 C₂₀H₁₆F₃N₃O: 371.36.

Example 24

5

(2-([(3-Chlorophenyl)methyl]amino}(3-pyridyl))-N-[3-(trifluoromethyl)phenyl]carboxamide

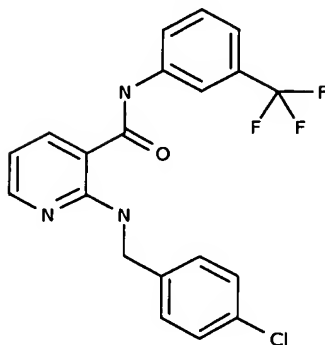
MS: (ES+) 406 (M+H); (ES-) 404. (M-H). Calc'd for
10 C₂₀H₁₅ClF₃N₃O: 405.81.

Example 25

15

(2-([(4-Bromophenyl)methyl]amino}(3-pyridyl))-N-[3-(trifluoromethyl)phenyl]carboxamide

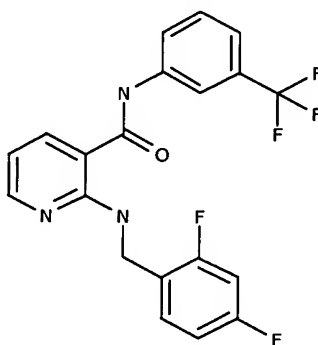
MS: (ES+) 451 (M+H); (ES-) 449. (M-H). Calc'd for
20 C₂₀H₁₅BrF₃N₃O: 450.26.

Example 26

5 **(2-[[4-Chlorophenyl)methyl]amino}(3-pyridyl))-N-[3-(trifluoromethyl)phenyl]carboxamide**

MS: (ES+) 406 (M+H); (ES-) 404. (M-H). Calc'd for
C₂₀H₁₅ClF₃N₃O: 405.81.

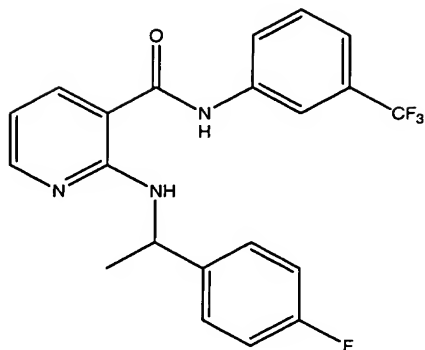
10

Example 27

15 **(2-[[2,4-Difluorophenyl)methyl]amino}(3-pyridyl))-N-[3-(trifluoromethyl)phenyl]carboxamide**

MS: (ES+) 408 (M+H); (ES-) 406. (M-H). Calc'd for
C₂₀H₁₇F₅N₃O: 407.34.

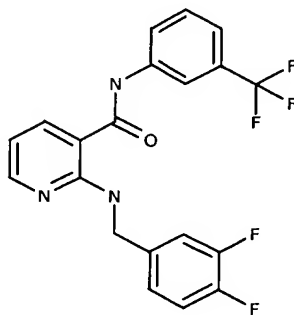
20

Example 28

5 **2-[1-(4-Fluoro-phenyl)-ethylamino]-N-(3-trifluoromethyl-phenyl)-nicotinamide**

MS: (ES+) 404 (M+H); (ES-) 402. (M-H). Calc'd for
C₂₁H₁₇F₄N₃O: 403.37.

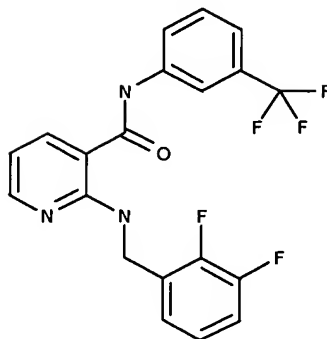
10

Example 29

15

(2-[[3,4-Difluorophenyl]methylamino](3-pyridyl))-N-[3-(trifluoromethyl)phenyl]carboxamide

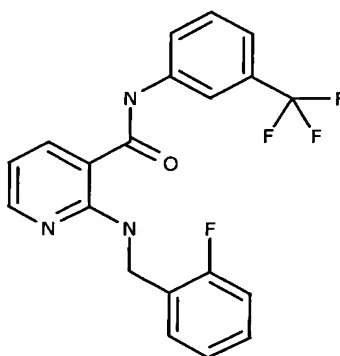
20 MS: (ES+) 408 (M+H); (ES-) 406. (M-H). Calc'd for
C₂₀H₁₄F₅N₃O: 407.34.

Example 30

5 **(2-((2,3-Difluorophenyl)methyl)amino)-N-[3-(trifluoromethyl)phenyl]carboxamide**

MS: (ES+) 408 (M+H); (ES-) 406. (M-H). Calc'd for
C₂₀H₁₄F₅N₃O: 407.34.

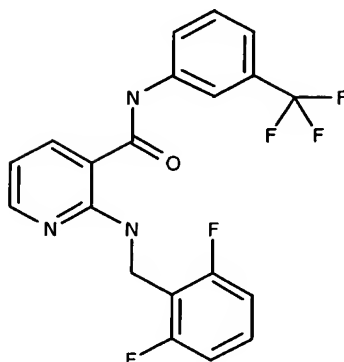
10

Example 31

15 **(2-((2-Fluorophenyl)methyl)amino)-N-[3-(trifluoromethyl)phenyl]carboxamide**

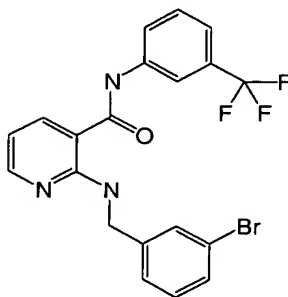
MS: (ES+) 390 (M+H); (ES-) 388. (M-H). Calc'd for
C₂₀H₁₅F₄N₃O: 389.35.

20

Example 32

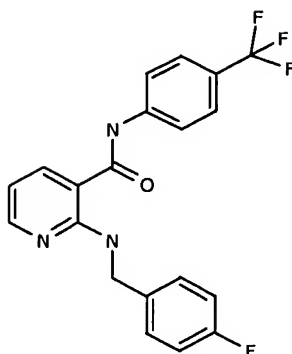
(2-[[2,6-Difluorophenyl)methyl]amino}(3-pyridyl))-N-[3-(trifluoromethyl)phenyl]carboxamide

MS: (ES+) 408 (M+H); (ES-) 406. (M-H). Calc'd for $C_{20}H_{14}F_5N_3O$: 407.34.

Example 33

(2-[[3-Bromophenyl)methyl]amino}(3-pyridyl))-N-[3-(trifluoromethyl)phenyl]carboxamide

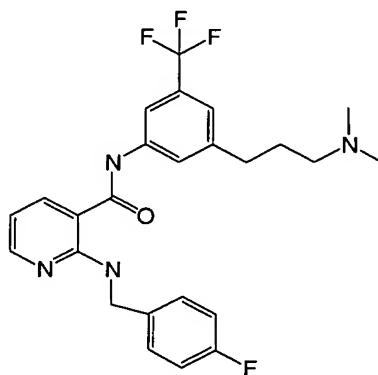
MS: (ES+) 451 (M+H); (ES-) 449. (M-H). Calc'd for $C_{20}H_{15}BrF_3N_3O$: 450.26.

Example 34

5 (2-[[4-(4-Fluorophenyl)methyl]amino](3-pyridyl))-N-[4-(trifluoromethyl)phenyl]carboxamide

MS: (ES+) 390 (M+H); (ES-) 388. (M-H). Calc'd for $C_{20}H_{15}F_4N_3O$: 389.35.

10

Example 35

15 N-{3-[3-(Dimethylamino)propyl]-5-(trifluoromethyl)phenyl}(2-[[4-(4-fluorophenyl)methyl]amino](3-pyridyl))carboxamide

Step A: Preparation of {3-[3-amino-5-(trifluoromethyl)phenyl]propynyl}dimethylamine

20 A mixture of 3-bromo-5-trifluoromethylaniline (1.4 g, 5.9 mmol), 1-dimethylamino-2-propyne (1.3 mL, 0.76 mmol),

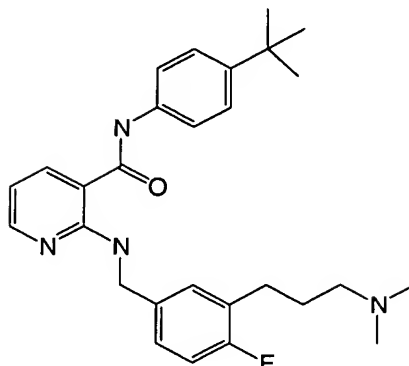
PdCl₂(PPh₃)₂ (0.26 g, 0.29 mmol) and CuI (114 mg, 0.60 mmol) in 10 mL of TEA was heated at 100 °C in a sealed tube for 3 h. The resulting mixture was filtered over Celite®. The filtrate was concentrated, and the residue was purified by
5 prep-HPLC (reverse phase) to give the aniline. MS (ES+): 243 (M+H)⁺; (ES-): 241 (M-H)⁻. Calc'd C₁₂H₁₃F₃N₂ - 242.24.

Step B: Preparation of {3-[3-amino-5-(trifluoromethyl)phenyl]propyl}dimethylamine

10 A mixture of the above aniline (7 g, 29 mmol) and Pd(OH)₂ (0.5 g) in 250 mL of MeOH was stirred under 50 psi H₂. After 2 h, the resulting mixture was filtered over Celite®. The filtrate was concentrated, and the residue was diluted with aq. 1 N HCl. The aq. layer was washed with
15 Et₂O, made basic with aq. 5 N NaOH, and extracted with CH₂Cl₂. The organic solution was dried over NaSO₄ and concentrated to give the titled compound. MS (ES+): 386 (M+H)⁺; (ES-): 384 (M-H)⁻. Calc'd C₁₈H₁₉ClF₃N₃O - 385.81.

20 **Step C: Preparation of N-{3-[3-(dimethylamino)propyl]-5-(trifluoromethyl)phenyl}(2-[[4-fluorophenyl)methyl]amino}(3-pyridyl)carboxamide**

The title compound was analogously synthesized by the method described in Example 7. MS (ES+): 475 (M+H)⁺; (ES-):
25 473 (M-H)⁻. Calc'd C₂₅H₂₆F₄N₄O - 474.50.

Example 36

5 **{2-[(3-{3-(Dimethylamino)propyl}-4-fluorophenyl)methyl]amino}(3-pyridyl)-N-[4-(tert-butyl)phenyl]carboxamide**

Step A: Preparation of N-Boc-(3-bromo-4-fluoro-benzyl)amine

10 To a solution of 3-bromo-4-fluorobenzylamine hydrochloride (10 g, 42 mmol) and TEA (10.5 g, 103 mmol) in 200 mL of CH₂Cl₂ was added BOC₂O (9.1g, 42 mmol) at RT. The resulting solution was stirred for 16 h. The solution was diluted with aq. 1 N NaOH and CH₂Cl₂. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated to
15 give N-Boc-(3-bromo-4-fluoro-benzyl)amine. MS (ES⁺): 305 (M+H)⁺; (ES⁻): 303 (M-H). Calc'd C₁₂H₁₅BrFNO₂ - 304.16.

Step B: Preparation of [3-(3-dimethylamino-propyl)-4-fluoro-benzyl]-Boc-amine

20 [3-(3-Dimethylamino-propyl)-4-fluoro-benzyl]-Boc-amine was prepared from N-Boc-(3-bromo-4-fluoro-benzyl)amine according to a procedure similar to that described in Example 35, Step A.

Step C: Preparation of N-{3-[3-(dimethylamino)propyl]-4-fluorophenyl}methylamine

To [3-(3-Dimethylamino-propyl)-4-fluoro-benzyl]-Boc-amine (3.0 g, 10 mmol) in 100 mL of CH₂Cl₂ was slowly added
5 TFA (10 mL). The resulting solution was stirred for 1 h,
then concentrated. The residue was diluted with CH₂Cl₂ and
aq. NaHCO₃ solution. The organic layer was dried over Na₂SO₄
and concentrated to give the title compound. MS (ES⁺): 211
(M+H)⁺; (ES⁻): 209 (M-H). Calc'd C₁₂H₁₉FN₂ - 210.29.

10

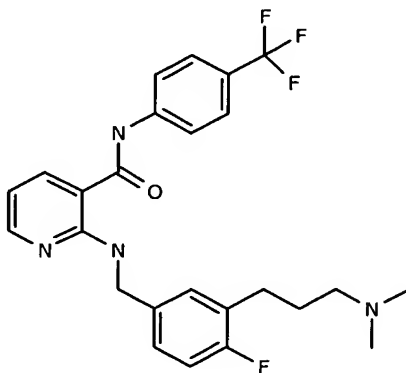
Step D: Preparation of {2-[(3-[3-(dimethylamino)propyl]-4-fluorophenyl)methyl]amino}(3-pyridyl)}-N-[4-(tert-butyl)phenyl]carboxamide

The title compound was analogously synthesized by the
15 method described in Example 7. MS (ES⁺): 463 (M+H)⁺; (ES⁻):
461 (M-H). Calc'd C₂₈H₃₅FN₄O - 462.61.

The following compounds were analogously synthesized
by the method described in Example 36.

20

Example 37



{2-[(3-[3-(Dimethylamino)propyl]-4-fluorophenyl)methyl]amino}(3-pyridyl)}-N-[4-(trifluoromethyl)phenyl]carboxamide

25

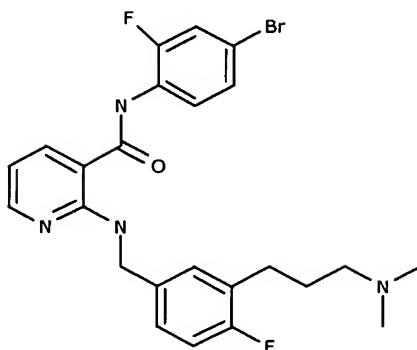
A-735C

- 261 -

MS (ES+): 475 (M+H)⁺; (ES-): 473 (M-H). Calc'd
C₂₅H₂₆F₄N₄O - 474.50.

Example 38

5



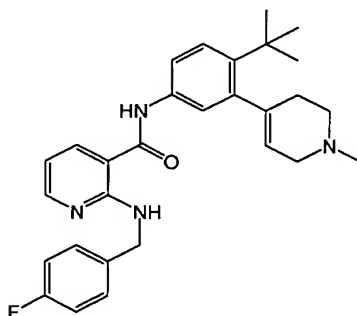
{2-[(3-[3-(Dimethylamino)propyl]-4-fluorophenyl)methylamino](3-pyridyl)}-N-(4-bromo-2-fluorophenyl)carboxamide

10

MS (ES+): 504 (M+H)⁺; (ES-): 502 (M-H). Calc'd C₂₄H₂₅BrF₂N₄O - 503.39.

15

Example 39



2-[(4-Fluorobenzyl)amino]-N-[4-tert-butyl-3-(1,2,3,6-tetrahydropyridin-4-yl)phenyl]nicotinamide

20

Step A: Preparation of 2-bromo-1-tert-butyl-4-nitrobenzene

NBS (125.0 g, 697.5 mmol, 1.5 eq) was slowly added to a solution of TFA:H₂SO₄ (5:1, 750 mL) and tert-butyl-4-nitrobenzene (100.0 g, 558.0 mmol) at RT. The solution was stirred for 24 h then poured over 5 kg of ice. The resulting suspension was filtered, washed with a 1:1 MeOH:H₂O solution (200 mL) and dried in a vacuum oven. MS (ES⁺): 258.1, 260.1 (M+H)⁺

10 **Step B: Preparation of 4-(2-tert-butyl-5-nitrophenyl)pyridine**

To a solution of 2-bromo-1-tert-butyl-4-nitrobenzene (8.6 g, 33.3 mmol) (Step A) and toluene (70 mL) in a 150 mL round bottom flask, 4-pyridylboronic acid (4.5 g, 36.6 mmol, 1.1 eq), Pd(PPh₃)₄ (3.8 g, 3.3 mmol, 0.1 eq) and K₂CO₃ (13.8 g, 99.9 mmol, 3 eq) were added. The solution was stirred for 24 h at 80°C. The solution was filtered through a pad of Celite® and purified by silica flash chromatography (30% Hex/Hex) to afford the desired compound as a yellow solid. MS (ES⁺): 257.2 (M+H)⁺; (ES⁻): 255.2 (M-H)⁻.

20 **Step C: Preparation of 4-(2-tert-butyl-5-nitrophenyl)-1-methylpyridinium**

4-(2-tert-Butyl-5-nitrophenyl)pyridine (2.0 g, 7.8 mmol) (Step B) was added to a round-bottom flask and dissolved in EtOH (10 mL). CH₃I (30 mL) was added to the flask and heated to reflux. After 6 h, the solution was cooled to RT and concentrated in vacuo resulting in the desired compound as a light brown solid. MS (ES⁺): 271.2 (M+H)⁺; (ES⁻): 269.2 (M-H)⁻. Calc'd for C₁₆H₁₉N₂O₂: 271.14.

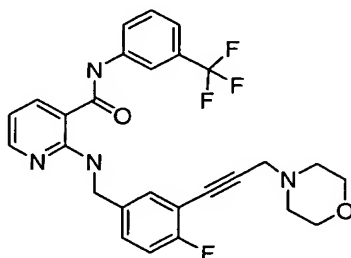
Step D: Preparation of 4-tert-butyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)aniline

4-(2-tert-Butyl-5-nitrophenyl)-1-methylpyridinium (2.1 g, 7.8 mmol) (Step C) was added to a 100 mL round-bottom flask and dissolved in a 10% H₂O/EtOH mixture. Iron dust (1.31 g, 23.4 mmol, 3 eq) and NH₄Cl (460 mg, 8.6 mmol, 1.1 eq) were added. The flask was heated to reflux. After 2 h, the solution was cooled to RT and filtered through a pad of Celite®. The resulting solution was stripped down to a yellow solid and redissolved in MeOH (20 mL, anhydrous). The solution was cooled to 0 °C and slowly adding NaBH₄ (450 mg, 11.7 mmol, 1.5 eq). The solution was cooled to RT and stirred for 30 min. The solvent was stripped-off under vacuum and the solid was redissolved in CH₂Cl₂ and filtered. The solution was concentrated *in vacuo* to afford an amorphous clear yellow solid. MS (ES+): 245.2 (M+H)⁺

Step E: Preparation of 2-[(4-fluorobenzyl)amino]-N-[4-tert-butyl-3-(1,2,3,6-tetrahydropyridin-4-yl)phenyl]nicotinamide

The title compound was analogously synthesized by the method described in Example 7. MS: (ES+) 473.2 (M+H); (ES-) 471.4 (M-H). Calc'd for C₂₉H₃₃FN₄O: 472.60.

Example 40



[2-([4-Fluoro-3-(3-morpholin-4-ylprop-1-ynyl)phenyl)methyl]amino)(3-pyridyl)]-N-[3-(trifluoromethyl)phenyl]carboxamide

5 **Step A: Preparation of (tert-butoxy)-N-[(3-bromo-4-fluorophenyl)methyl] carboxamide**

To a solution of 3-bromo-4-fluorobenzylamine (10 g, 41 mmol) and TEA (14 mL, 104 mmol) in CH₂Cl₂ was added BOC₂O (9.1 g, 41 mmol). The resulting solution was stirred for 16
10 h at RT, then diluted with aq. 1 N NaOH and CH₂Cl₂. The organic layer was separated, washed with brine, dried over Na₂SO₄, and concentrated to give (tert-butoxy)-N-[(3-bromo-4-fluorophenyl)methyl]carboxamide.

15 **Step B: Preparation of (tert-Butoxy)-N-{[4-fluoro-3-(3-hydroxyprop-1-ynyl)phenyl]methyl}carboxamide**

A mixture of tert-butoxy-N-[(3-bromo-4-fluorophenyl)methyl] carboxamide (0.6 g, 2.0 mmol, Step A), CuI (38 mg, 0.2 mmol), PdCl₂(PPh₃)₂ (72 mg, 0.1 mmol),
20 propargyl alcohol (0.35 mL, 6.0 mmol) and TEA (12 mL) was heated at 100 °C for 5 h. The resulting mixture was filtered, and the filtrate was concentrated. The residue was purified by SiO₂ chromatography to give the title compound.
MS (ES⁺): 297 (M+NH₄)⁺. Calc'd C₁₅H₂₂FN₂O₃ - 297.34.

25

Step C: Preparation of [4-Fluoro-3-(3-morpholin-4-ylprop-1-ynyl)phenyl]-methylaniline

To a mixture of (tert-butoxy)-N-{[4-fluoro-3-(3-hydroxyprop-1-ynyl)phenyl]methyl}carboxamide (0.23g, 0.82
30 mmol) (Step B) and NMO (0.14 g, 1.3 mmol) was added catalytic amount of TPAP. The resulting mixture was stirred for 1 h at RT, then filtered over a short pad of SiO₂ and concentrated. To a solution of the residue and morpholine (0.1 mL, 1.2 mmol) in CH₂Cl₂ was added excess NaBH(OAc)₃.

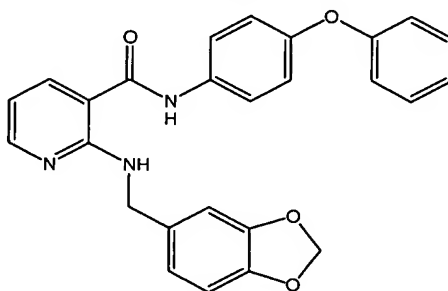
The resulting solution was stirred for 16 h, diluted with CH_2Cl_2 and saturated aq. NaHCO_3 solution. The organic layer was separated, dried over Na_2SO_4 , and concentrated. The residue was purified by SiO_2 chromatography to give a colorless oil, which was dissolved in 5 mL of CH_2Cl_2 . To the organic solution was added TFA (2 mL). The resulting solution was stirred for 1 h at RT, then concentrated. The residue was diluted with CH_2Cl_2 and saturated aq. NaHCO_3 solution. The organic layer was separated, dried over Na_2SO_4 , and concentrated to give the title compound. MS (ES+): 249 (M+H)⁺; (ES-): 247. Calc'd $\text{C}_{14}\text{H}_{17}\text{FN}_2\text{O}$ - 248.30.

Step D: Preparation of [2-([4-fluoro-3-(3-morpholin-4-ylprop-1-ynyl)phenyl]methyl)amino](3-pyridyl)]-N-[3-(trifluoromethyl)phenyl]carboxamide

The title compound was analogously synthesized by the method described in Example 7. MS (ES+): 513 (M+H)⁺; (ES-): 511. Calc'd $\text{C}_{27}\text{H}_{24}\text{F}_4\text{N}_4\text{O}_2$ - 512.51.

20

Example 41

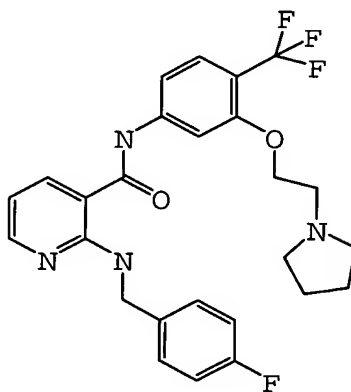


{2-[(2H-Benzo[d]1,3-dioxol-5-ylmethyl)amino](3-pyridyl)]-N-(4-phenoxyphenyl)carboxamide:

25

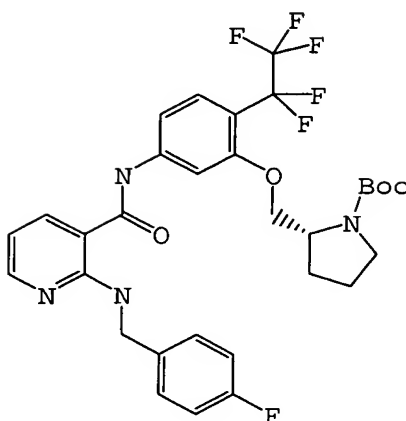
2-Chloro-(3-pyridyl)-N-(4-phenoxyphenyl)-carboxamide (0.500 g, 1.5 mmol) and 2H-benzo[d]1,3-dioxolan-5-ylmethanamine (0.680 g, 4.5 mmol) were combined and heated neat at 110 °C for 18 h. After cooling to RT, the resulting

residue was dissolved in EtOAc and washed with saturated Na₂CO₃ solution and brine, respectively. The organics were dried over Na₂SO₄ and evaporated. The crude material was purified by column chromatography with EtOAc/hexanes (1:2) as eluant to leave the desired compound as an off-white solid. MS: (ES+) 440 (M + 1)⁺; (ES-): 438 (M - 1)⁻. Calc'd. for C₂₆H₂₁N₃O₄ - 439.15.

Example 42

2-(4-Fluoro-benzylamino)-N-[3-(2-pyrrolidin-1-yl-ethoxy)-4-trifluoromethyl-phenyl]-nicotinamide

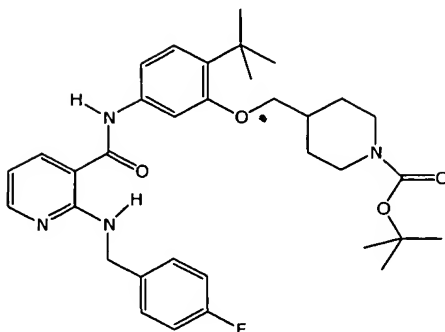
2-Chloro-N-[3-(2-pyrrolidin-1-yl-ethoxy)-4-trifluoromethyl-phenyl]-nicotinamide (199.1 mg), DIEA (252 μ L) and 4-fluorobenzylamine (193 μ L) were combined in a sealed tube and heated to 130 $^{\circ}$ C for 2 h. The mixture was purified on silica gel chromatography (2-3.5% MeOH/CH₂Cl₂). The desired fractions were concentrated *in vacuo*, and the residue was dissolved in Et₂O and hexanes were added until the solution became cloudy. The solids were filtered, and dried. Additional material was obtained from the filtrate upon additional rounds of concentration, dissolving in Et₂O and treatment with hexanes. M+H 503.4, Calc'd for C₂₆H₂₆N₄O₂F₄ - 502.2.

Example 43

5

(R) 2-(4-Fluoro-benzylamino)-N-[3-(1-Boc-pyrrolidin-2-ylmethoxy)-4-pentafluoroethyl-phenyl]-nicotinamide

2-Chloro-N-[3-(1-Boc-pyrrolidin-2-ylmethoxy)-4-pentafluoroethyl-phenyl]-nicotinamide (442.8 mg) DIEA (351 μ L) and 4-fluorobenzylamine (322 μ L) were combined in a sealed tube and heated to 130 °C for 3 h. The mixture was diluted with EtOAc and H₂O, the layers were separated and the organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified with silica gel chromatography (1% MeOH/CH₂Cl₂) to obtain an off-white solid.

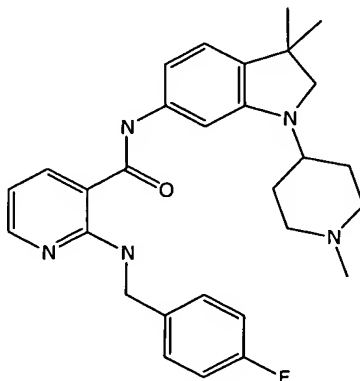
Example 44

5

N-[4-tert-Butyl-3-(1-Boc-piperidin-4-ylmethoxy)-phenyl]-2-(4-fluorobenzylamino)-nicotinamide

N-[4-tert-Butyl-3-(1-Boc-piperidin-4-ylmethoxy)-phenyl]-2-chloro-nicotinamide (200 mg), DIEA (145 μ L), IpOH (3 mL) and 4-fluorobenzylamine (184 μ L) were combined in a sealed tube and heated to 125 $^{\circ}$ C for 2 days. The mixture was purified by flash chromatography (EtOAc) to provide the product. M+Na 619; Calc'd for $C_{34}H_{43}FN_4O_4$: 590.33.

15

Example 45

N-[3,3-Dimethyl-1-(1-methyl-piperidin-4-yl)-2,3-dihydro-1H-indol-6-yl]-2-(4-fluoro-benzylamino)-nicotinamide

5 A solution of N-[3,3-dimethyl-1-(1-methyl-piperidin-4-yl)-2,3-dihydro-1H-indol-6-yl]-2-fluoro-nicotinamide (500 mg), 4-fluorobenzylamine (240 μ L) and NaHCO₃ (359 mg) was dissolved in IpOH (5 mL) and heated to 85 °C overnight. After cooling to RT, the mixture was dried under N₂. The
10 residue was partitioned between EtOAc and H₂O, the organic layer was separated, washed with brine, dried over Na₂SO₄ and filtered. Silica was added to the filtrate and concentrated to a residue. It was purified by flash chromatography (10% MeOH/EtOAc) to yield a fluffy yellow
15 solid. M+H 488.4. Calc'd for C₂₉H₃₄FN₅O: 487.3.

 The following compounds (Examples 46-53) were analogously formed from the corresponding fluoro compounds by the method described in Example 45.

20

46) N-[1-(2-Dimethylamino-acetyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl]-2-(4-fluoro-benzylamino)-nicotinamide. M+H 476.3; Calc'd 475.24.

25 47) N-[1-(1-Boc-piperidin-4-yl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl]-2-(4-fluoro-benzylamino)-nicotinamide. M+H 574.5; Calc'd 573.31.

 48) N-[3,3-Dimethyl-1-(2-Boc-amino-acetyl)-2,3-dihydro-1H-indol-6-yl]-2-(4-fluoro-benzylamino)-nicotinamide. M+H
30 548.4.

49) 2-(4-Fluoro-benzylamino)-N-(2-Boc-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-nicotinamide. M+H 505.4.

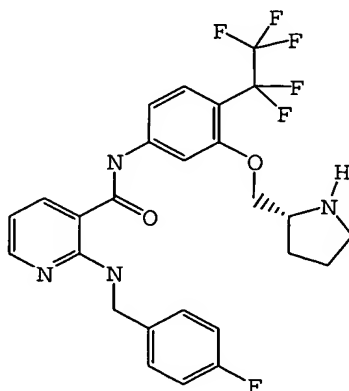
50) N-[3-(1-Boc-pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-2-(4-fluoro-benzylamino)-nicotinamide was prepared as above but at 90C overnight and with a second addition of
5 amine prior to heating for another 24 h. M+Na 611. Calc'd 588.2.

51) N-[4-tert-Butyl-3-(1-Boc-pyrrolidin-2-ylmethoxy)-phenyl]-2-(4-fluoro-benzylamino)-nicotinamide. M+Na 599.
10 Calc'd 576.31.

52) N-(4-Acetyl-2,2-dimethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-2-(4-fluoro-benzylamino)-nicotinamide was prepared as described above but substituting t-BuOH for
15 IpOH and heating overnight at 80C. M+H 449.1; Calc'd 448.19.

53) 2-(4-Fluoro-benzylamino)-N-[3-(1-Boc-piperidin-4-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide. M+H
20 603.4.

Example 54



25 **(R) 2-(4-Fluoro-benzylamino)-N-[3-(pyrrolidin-2-ylmethoxy)-4-pentafluoroethyl-phenyl]-nicotinamide**

2-(4-Fluoro-benzylamino)-N-[3-(1-Boc-pyrrolidin-2-ylmethoxy)-4-pentafluoroethyl-phenyl]-nicotinamide (Example 43) was dissolved in CH₂Cl₂ (8 mL) and TFA (8 mL) was added. After stirring at RT for 70 min, the mixture was
5 concentrated *in vacuo*, diluted with 2N NaOH and CH₂Cl₂. The layers were separated and the aqueous layer was back extracted with CH₂Cl₂. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to provide an light pink-orange solid. M+H 539.5. Calc'd
10 for C₂₆H₂₄F₆N₄O₂: 538.2.

The following compounds (Examples 55-59) were analogously formed from the corresponding Boc-protected compounds by the method described in Example 54.

15

55) (R) 2-(4-Fluoro-benzylamino)-N-[3-(pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide. M+H 489; Calc'd 488.2.

20

56) N-[4-tert-Butyl-3-(piperidin-4-ylmethoxy)-phenyl]-2-(4-fluoro-benzylamino)-nicotinamide. M+H 491; Calc'd 490.3.

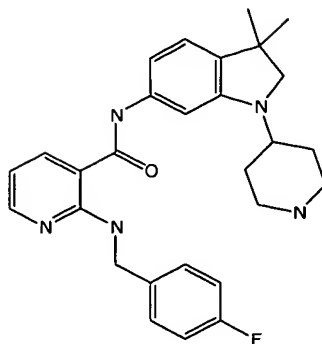
25

57) (R) N-[4-tert-Butyl-3-(pyrrolidin-2-ylmethoxy)-phenyl]-2-(4-fluoro-benzylamino)-nicotinamide. M+H 477; Calc'd
476.3.

30

58) N-(4,4-Dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-(4-fluoro-benzylamino)-nicotinamide. M+H 405.1; Calc'd
404.2.

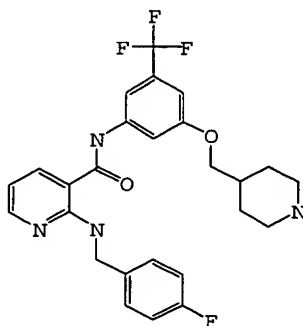
59) N-[1-(2-Amino-acetyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl]-2-(4-fluoro-benzylamino)-nicotinamide.

Example 60

5 **N-(3,3-Dimethyl-1-piperidin-4-yl)-2,3-dihydro-1H-indol-6-yl)-
2-(4-fluorobenzylamino)-nicotinamide**

N-[1-(1-Boc-piperidin-4-yl)-3,3-dimethyl-2,3-dihydro-
1H-indol-6-yl]-2-(4-fluorobenzylamino)-nicotinamide

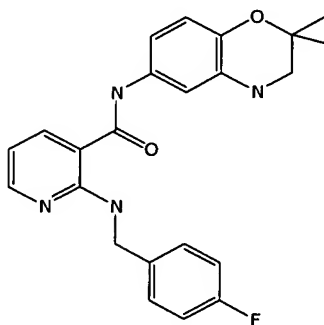
10 (Example 47) was dissolved in a mixture of conc. HCl and
EtOAc and stirred at RT for 1.5 h. The mixture was
concentrated *in vacuo* and the residue was partitioned
between EtOAc and 1 N NaOH. The organic layer was removed,
washed with brine, dried over Na₂SO₄, filtered and
15 concentrated *in vacuo* to provide a yellow solid. M+H 474.3.
Calc'd for C₂₈H₃₂FN₅O: 473.3.

Example 61

2-(4-Fluoro-benzylamino)-N-[3-(piperidin-4-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide

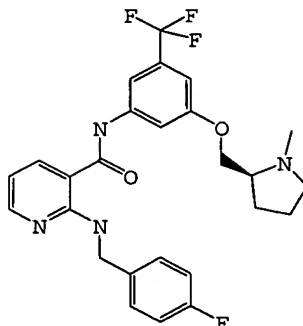
2-(4-Fluoro-benzylamino)-N-[3-(piperidin-4-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide was prepared by a method similar to that described for Example 60. M+H 503.3. Calc'd for $C_{26}H_{26}F_4N_4O_2$: 502.2.

Example 62



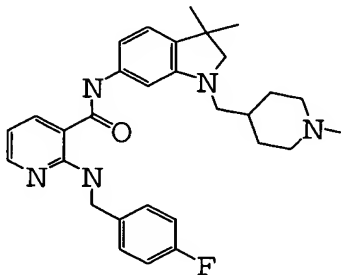
N-(2,2-Dimethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-2-(4-fluoro-benzylamino)-nicotinamide

N-(4-Acetyl-2,2-dimethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-2-(4-fluoro-benzylamino)-nicotinamide (250 mg, Example 52) was dissolved in EtOH (10 mL) and treated with conc. HCL (0.5 mL) at 60 °C for 16 h. The mixture was cooled to 0 °C and sat. $NaHCO_3$ (aq) was added. The mixture was extracted with EtOAc (3 x 50 mL) and the combined organic fractions were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (50% EtOAc/hexanes). M+H 407.3; Calc'd for $C_{23}H_{23}FN_4O_2$: 406.18.

Example 63

5 **(S)-2-(4-Fluoro-benzylamino)-N-[3-(1-methyl-pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide**

2-Fluoro-N-[3-(1-methyl-pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide (300 mg), TEA (314 μ L)
 10 and 4-fluorobenzylamine (170 μ L) were combined in a sealed tube and heated to 90 $^{\circ}$ C for 3 h. Cooled to RT and the mixture was diluted with EtOAc, washed with sat. NH_4Cl (2x), brine, dried over Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by silica gel chromatography
 15 ($\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$ 95/5/0.5) to provide an off-white foam upon drying. M+H 503. Calc'd for $\text{C}_{26}\text{H}_{26}\text{F}_4\text{N}_4\text{O}_2$: 502.20.

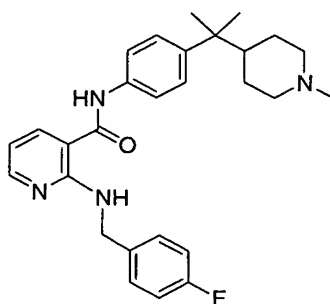
Example 64

20

N-[3,3-Dimethyl-1-(1-methyl-piperidin-4-ylmethyl)-2,3-dihydro-1H-indol-6-yl]-2-(4-fluoro-benzylamino)-nicotinamide

To N-(3,3-dimethyl-1-piperidin-4-ylmethyl-2,3-dihydro-1H-indol-6-yl)-2-(4-fluoro-benzylamino)-nicotinamide (0.92 g) dissolved in DCE (20 mL) at RT was added formaldehyde (37% aqueous, 0.42 mL) followed by NaBH(OAc)₃ (1.59 g). After 4 h, the mixture was quenched with 1 N HCl (20 mL) and H₂O (20 mL). It was basified with sat NaHCO₃, extracted with CH₂Cl₂ (3 x 50 mL) and the combined extracts were washed with brine, dried (K₂CO₃) and concentrated onto SiO₂ (previously treated with 10% MeOH (2 M NH₃ in MeOH/CH₂Cl₂ and then concentrated *in vacuo*). The residue was purified by flash chromatography (Isco, 35g column, 1-7% MeOH (2M NH₃ in MeOH/CH₂Cl₂). The bulk of the crude yellow material was further purified by reverse phase Prep HPLC. The isolated fractions were partially concentrated and basified with 1 N NaOH and dried under vacuum to afford a slightly yellow powder. M+H=502.3. Calc'd for C₃₀H₃₆FN₅O: 501.29.

Example 65

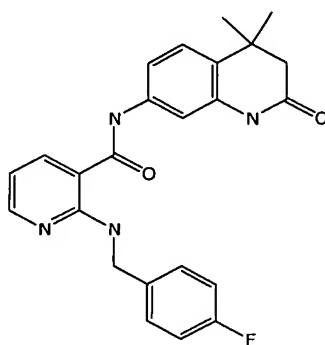


2-(4-Fluoro-benzylamino)-N-{4-[1-methyl-1-(1-methyl-1-piperidin-4-yl)-ethyl]-phenyl}-nicotinamide

25

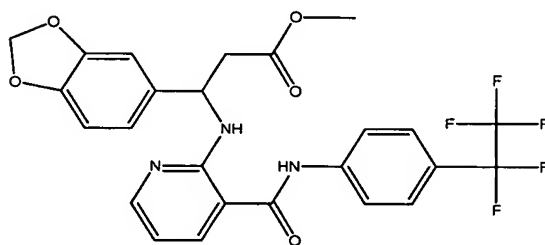
A solution of 2-fluoro-N-{4-[1-methyl-1-(1-methyl-1-piperidin-4-yl)-ethyl]-phenyl}-nicotinamide (355 mg) and 4-fluorobenzylamine (250 mg) in pyridine (10 mL) was suspended with NaHCO₃ (1 g). The mixture was heated to 105 °C

overnight. Solids were removed by filtration and the filtrate was concentrated *in vacuo*. The residue was purified on prep. TLC plates (silica, EtOAc:TEA=10:1) to provide the desired product. MS (ES⁺): 461 (M+1)⁺, Calc'd for C₂₈H₃₃FN₄O - 460.59.

Example 66

N-(4,4-Dimethyl-2-oxo-1,2,3,4-tetrahydro-quinolin-7-yl)-2-(4-fluorobenzylamino)-nicotinamide

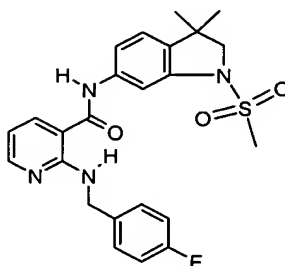
M+H 419.1. Calc'd for C₂₄H₂₃FN₄O₂: 418.2.8

Example 67

3-Benzo[1,3]dioxol-5-yl-3-[3-(4-pentafluoroethylphenylcarbamoyl)-pyridin-2-ylamino]-propionic acid

The Compound was synthesized by a procedure similar to the method described in Example 45. M+H 524.1. Calc'd for $C_{25}H_{20}F_5N_3O_5$: 537.13.

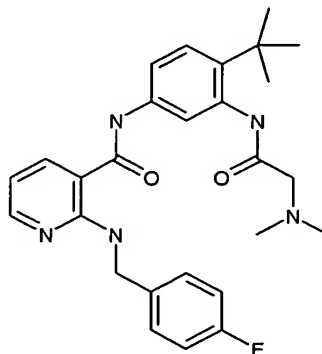
5

Example 68

10 **N-(3,3-Dimethyl-1-(methylsulfonyl)-2,3-dihydro-1H-indol-6-yl)-2-(((4-fluorophenyl)methyl)amino)-3-pyridinecarboxamide**

Calc'd for $C_{24}H_{25}FN_4O_3S$ - 468.55; M+H - 469.1.

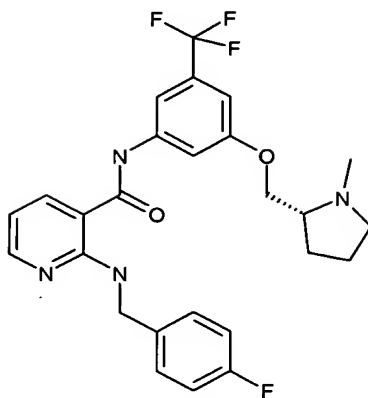
15

Example 69

20

N-(4-(1,1-Dimethylethyl)-3-((N,N-dimethylglycyl)amino)phenyl)-2-(((4-fluorophenyl)methyl)amino)-3-pyridinecarboxamide

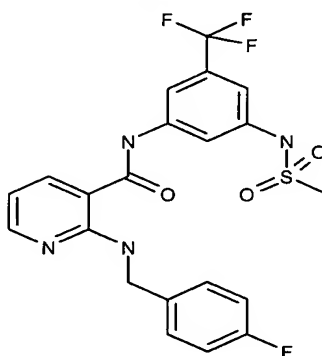
Calc'd for $C_{27}H_{32}FN_5O_2$ - 477.581; M+H 478.

Example 70

5

2-(((4-Fluorophenyl)methyl)amino)-N-(3-(((2R)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-3-pyridinecarboxamide

10 $C_{26}H_{26}F_4N_4O_2$ - 502.509; M+H 503.

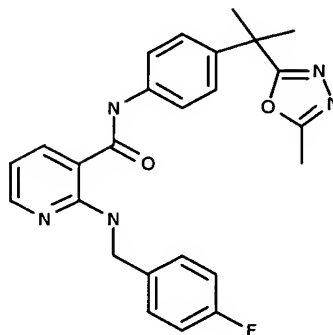
Example 71

15

2-(((4-Fluorophenyl)methyl)amino)-N-(3-((methylsulfonyl)amino)-5-(trifluoromethyl)phenyl)-3-pyridinecarboxamide

20

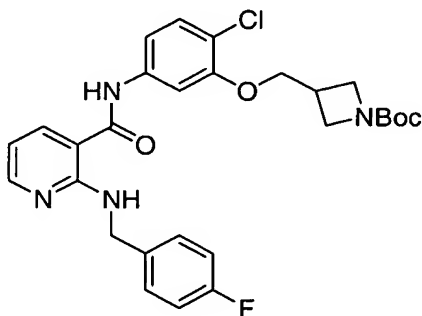
$C_{21}H_{18}F_4N_4O_3S$ - 482.456; M+H 483, M+Na 505. ,

Example 72

5 **2-(((4-Fluorophenyl)methyl)amino)-N-(4-(1-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)phenyl)-3-pyridinecarboxamide**

MS: 446 (M+1); Calc'd for C₂₅H₂₅FN₅O₂ - 445.19.

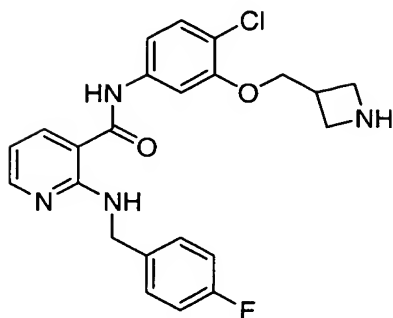
10

Example 73

15 **3-(2-Chloro-5-([2-(4-fluoro-benzylamino)-pyridine-3-carbonyl]-amino)-phenoxy)methyl)-azetidine-1-carboxylic acid tert-butyl ester**

MS (ES⁺): 542 (M+H)⁺. Calc'd for C₂₈H₃₀ClFN₄O₄ - 541.02

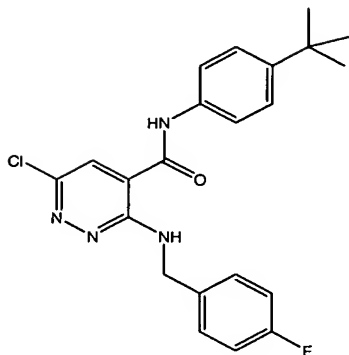
20

Example 74

5

N-[3-(Azetidin-3-ylmethoxy)-4-chloro-phenyl]-2-(4-fluoro-benzylamino)-nicotinamide

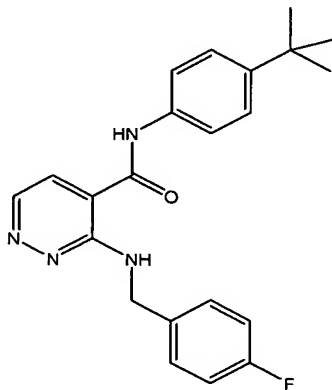
To a solution of 10 mL of TFA/CH₂Cl₂ (1:1) was added 3-
10 (2-chloro-5-{[2-(4-fluoro-benzylamino)-pyridine-3-carbonyl]-
amino}-phenoxy)methyl)-azetidine-1-carboxylic acid tert-butyl
ester (270 mg, 0.5 mmol) at 0 °C. The solution was stirred
for 2 h at RT. The solvents were removed *in vacuo*. The
residue was diluted in 30 mL of EtOAc and washed with 30 mL
15 of saturated aqueous NaHCO₃, then brine. The resulting
organic phase was dried over MgSO₄ and concentrated *in*
vacuo. The title compound was purified by column
chromatography (silica gel, 5% 2N NH₃ in MeOH/ EtOAc) and
isolated as a white solid. MS (ES⁺): 442 (M+H)⁺. Calc'd
20 for C₂₃H₂₂ClFN₄O₂ - 440.90.

Example 75

5

**6-Chloro-3-(4-fluoro-benzylamino)-pyridazine-4-carboxylic
acid (4-tert-butyl-phenyl)-amide**

A mixture of 3-(benzotriazol-1-yloxy)-6-chloro-
10 pyridazine-4-carboxylic acid (4-tert-butyl-phenyl)-amide
(0.348 g, 0.82 mmol) and 4-fluorobenzylamine (1.0 mL, 8.75
mmol) was stirred at 60 °C under N₂ for 30 min, cooled to
RT, and purified by flash column chromatography. The desired
compound was obtained as a solid. MS (ES⁺): 413.0 (M+H)⁺.
15 Calc'd for C₂₂H₂₂ClFN₄O - 412.89.

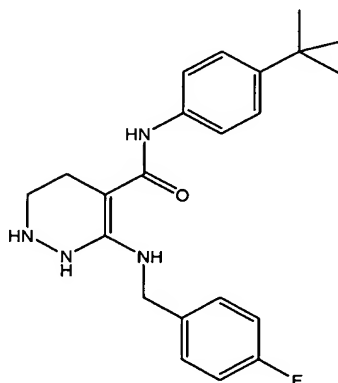
Example 76

20

3-(4-Fluoro-benzylamino)-pyridazine-4-carboxylic acid (4-tert-butyl-phenyl)-amide

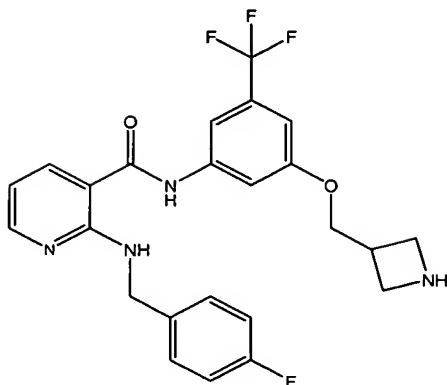
A mixture of 6-chloro-3-(4-fluoro-benzylamino)-pyridazine-4-carboxylic acid (4-tert-butyl-phenyl)-amide (0.210 g, 0.51 mmol) and Pd/C (50 mg, 10% weight) in 10 mL of MeOH was placed under H₂ from a balloon and stirred at RT for 26 h, filtered through Celite®, condensed, and purified by flash column chromatography (0.5% to 2% of MeOH in CH₂Cl₂, then 1% of MeOH and 1% of NH₄OH in CH₂Cl₂). The titled product was obtained as a light yellowish solid. MS (ES⁺): 379.0 (M+H)⁺. Calc'd for C₂₂H₂₃FN₄O - 378.44.

Example 77



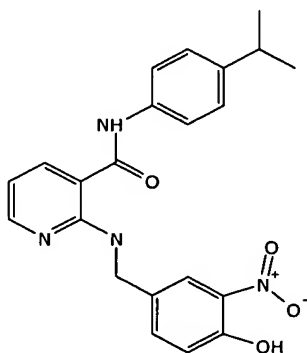
3-(4-Fluoro-benzylamino)-1,2,5,6-tetrahydro-pyridazine-4-carboxylic acid (4-tert-butyl-phenyl)-amide

The titled compound was prepared in the same method as that of Example 76, and isolated as a light yellowish solid. MS (ES⁺): 383.0 (M+H)⁺. Calc'd for C₂₁H₂₃N₅O - 382.47.

Example 78

5 **N-[3-(Azetidin-3-ylmethoxy)-5-trifluoromethyl-phenyl]-2-(4-**
 fluoro-benzylamino)-nicotinamide

The title compound was synthesized from 3-(3-amino-5-trifluoromethyl-phenoxy-methyl)-azetidine-1-carboxylic acid
10 benzyl ester analogous to that described for Example 74. MS
 (ES⁺): 475.1 (M+H)⁺. Calc'd. for C₂₈H₃₄N₄O - 474.5.

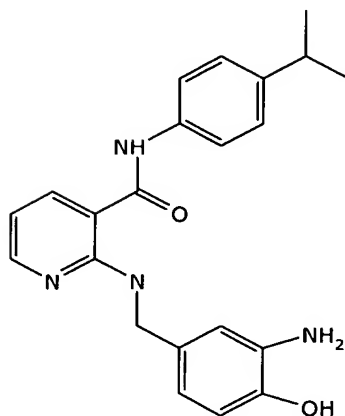
Example 79

15

2-(4-Hydroxy-3-nitro-benzylamino)-N-(4-isopropyl-phenyl)-
 nicotinamide

MS: (ES+) 407 (M+H). Calc'd for $C_{22}H_{22}N_4O_4$ - 406.45.

Example 80

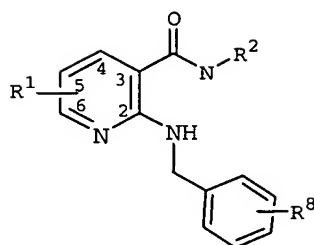


5

**2-(4-Hydroxy-3-amino-benzylamino)-N-(4-isopropyl-phenyl)-
nicotinamide**

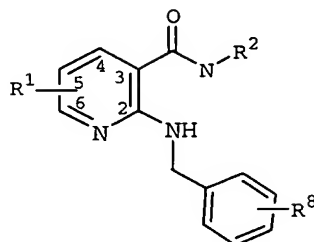
10 MS: (ES+) 377 (M+H). Calc'd for $C_{22}H_{24}N_4O_2$ - 376.45.

Other compounds included in this invention are set forth in Tables 1-3 below.

Table 1

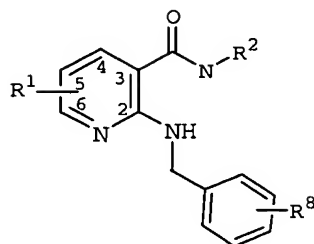
5	#	R ¹	R ²	R ⁸
	81.	4-chlorophenyl	H	4-amino-
	82.	3-isoquinolinyl	H	
	83.	2-quinolinyl	H	
10	84.	2-benzthiazolyl	H	
	85.	2-benzimidazolyl	H	4-amino-
	86.	4-benzimidazolyl	H	
	87.	5-benzimidazolyl	H	
	88.	6-benzimidazolyl	H	
15	89.	7-benzimidazolyl	H	
	90.	2-chlorophenyl	5-Br	
	91.	3-isoquinolinyl	5-Br	
	92.	2-quinolinyl	5-Br	
	93.	2-benzthiazolyl	5-Br	
20	94.	2-benzimidazolyl	5-Br	
	95.	4-benzimidazolyl	5-Br	
	96.	5-benzimidazolyl	5-Br	
	97.	6-benzimidazolyl	5-Br	4-amino-
	98.	7-benzimidazolyl	5-Br	4-amino-
25	99.	4-chlorophenyl	5-Br	3-amino
	100.	4-chlorophenyl	5-Br	4-hydroxy
	101.	4-chlorophenyl	6-CH ₃	4-amino-

Table 1 (cont.)



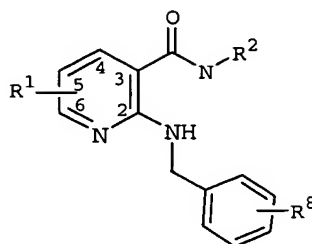
5	#	R ²	R ¹	R ⁸
	102.	4-phenoxyphenyl	H	4-amino
	103.	3-phenoxyphenyl	H	4-methoxy
	104.	4-biphenyl	H	4-methoxy
	105.	4-cyclohexylphenyl	H	4-methoxy
10	106.	2-quinolyl	H	4-methoxy
	107.	3-isoquinolyl	H	4-methoxy
	108.	3-quinolyl	H	4-methoxy
	109.	1-isoquinolyl	H	4-methoxy
	110.	5-quinolyl	H	4-methoxy
15	111.	5-isoquinolyl	H	4-methoxy
	112.	6-quinolyl	H	4-methoxy
	113.	6-isoquinolyl	H	4-methoxy
	114.	7-quinolyl	H	4-methoxy
	115.	7-isoquinolyl	H	4-hydroxy
20	116.	4-quinolyl	H	4-hydroxy
	117.	4-isoquinolyl	H	4-hydroxy
	118.	4-pyridyl	H	4-hydroxy
	119.	4-pyrimidinyl	H	4-hydroxy
	120.	2-pyrimidinyl	H	4-hydroxy
25	121.	6-pyrimidinyl	H	4-hydroxy
	122.	4-pyridazinyl	H	4-hydroxy
	123.	5-pyridazinyl	H	4-hydroxy
	124.	4-indolyl	H	4-hydroxy
	125.	5-isoindolyl	H	3-amino
30	126.	5-naphthyridinyl	H	3-amino
	127.	6-quinozalinyl	H	3-amino

Table 1 (cont.)

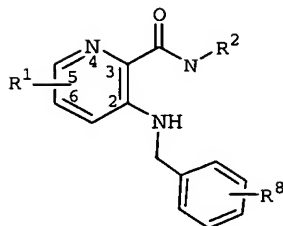


5	#	R ²	R ¹	R ⁸
	128.	6-isoquinolyl	H	3-amino
	129.	4-naphthyridinyl	H	3-amino
	130.	5-quinoxaliny	H	3-amino
	131.	4-naphthyridinyl	H	3-amino
10	132.	3,4-dichlorophenyl	H	2-cyano
	133.	6-isoquinolyl	H	2-cyano
	134.	4-chlorophenyl	H	3-cyano
	135.	4-chlorophenyl	H	4-cyano
	136.	6-indazolyl	H	3-hydroxymethyl
15	137.	6-isoindolyl	H	3-hydroxymethyl
	138.	5-indazolyl	H	3-hydroxymethyl
	139.	5-isoindolyl	H	3-hydroxymethyl
	140.	6-benzothienyl	H	3-hydroxymethyl
	141.	6-benzofuryl	H	3-hydroxymethyl
20	142.	5-benzothienyl	H	3-hydroxymethyl
	143.	5-benzofuryl	H	3-hydroxymethyl
	144.	2-benzimidazolyl	H	3-hydroxymethyl
	145.	2-benzoxazolyl	H	3-hydroxymethyl
	146.	6-benzimidazolyl	H	3-hydroxymethyl
25	147.	6-benzoxazolyl	H	3-hydroxymethyl
	148.	6-benzthiazolyl	H	4-amino
	149.	2-quinazolinyl	H	4-hydroxymethyl
	150.	3-(phenoxy)-6-pyridyl	H	3-aminocarbonyl
	151.	4-(phenylcarbonyl)phenyl	H	3-aminocarbonyl

Table 1 (cont.)

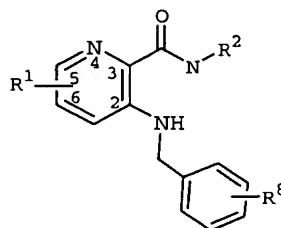


5	#	R^2	R^1	R^8
	152.	4-(phenylamino)phenyl	H	3-aminocarbonyl
	153.	4-cyclohexyloxyphenyl	H	3-aminocarbonyl
	154.	4-(3-thienyl)phenyl	H	4-amino
	155.	4-(pyrazol-3-yl)phenyl	H	4-amino
10	156.	4-pyridyl	6-Cl	4-amino, 3-F
	157.	3-methoxyphenyl	6-Cl	4-amino, 3-F
	158.	4-hydroxyphenyl	6-Cl	4-amino, 3-F
	159.	3-hydroxyphenyl	H	4-methoxy, 3-F
	160.	2-hydroxyphenyl	H	3-methoxy, 3-F
15	161.	4-chlorophenyl	6-phenyl	4-amino
	162.	4-phenoxyphenyl	6-phenyl	4-amino
	163.	4-biphenyl	6-phenyl	4-amino
	164.	4-hydroxyphenyl	6-phenyl	4-amino
	165.	4-cyclohexylphenyl	6-phenyl	4-amino
20	166.	3-isoquinolyl	6-phenyl	4-amino

Table 2

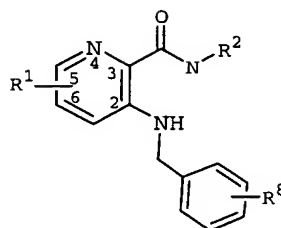
5	#	R^8	R^2	R^1
	154.	4-amino-	4-chlorophenyl	H
	155.	4-amino-	3-isoquinolinyl	H
	156.	4-amino-	2-quinolinyl	H
	157.	4-amino-	2-benzthiazolyl	H
10	158.	4-amino-	2-benzimidazolyl	H
	159.	4-amino-	4-benzimidazolyl	H
	160.	4-amino-	5-benzimidazolyl	H
	161.	4-amino-	6-benzimidazolyl	H
	162.	4-amino-	7-benzimidazolyl	H
15	163.	4-amino-	2-chlorophenyl	5-Br
	164.	4-amino-	3-isoquinolinyl	5-Br
	165.	4-amino-	2-quinolinyl	5-Br
	166.	4-amino-	2-benzthiazolyl	5-Br
	167.	4-amino-	2-benzimidazolyl	5-Br
20	168.	4-amino-	4-benzimidazolyl	5-Br
	169.	4-amino-	5-benzimidazolyl	5-Br
	170.	4-amino-	6-benzimidazolyl	5-Br
	171.	4-amino-	7-benzimidazolyl	5-Br
	172.	3-amino-	4-chlorophenyl	5-Br
25	173.	4-hydroxy-	4-chlorophenyl	5-Br
	174.	4-amino-	4-chlorophenyl	6-CH ₃

Table 2 (cont.)



5	#	R ²	R ¹	R ⁸
	175.	4-phenoxyphenyl	H	4-amino
	176.	3-phenoxyphenyl	H	4-methoxy
	177.	biphenyl	H	4-methoxy
	178.	4-cyclohexylphenyl	H	4-methoxy
10	179.	2-quinolyl	H	4-methoxy
	180.	3-isoquinolyl	H	4-methoxy
	181.	3-quinolyl	H	4-methoxy
	182.	1-isoquinolyl	H	4-methoxy
	183.	5-quinolyl	H	4-methoxy
15	184.	5-isoquinolyl	H	4-methoxy
	185.	6-quinolyl	H	4-methoxy
	186.	6-isoquinolyl	H	4-methoxy
	187.	7-quinolyl	H	4-methoxy
	188.	7-isoquinolyl	H	4-hydroxy
20	189.	4-quinolyl	H	4-hydroxy
	190.	4-isoquinolyl	H	4-hydroxy
	191.	4-pyridyl	H	4-hydroxy
	192.	4-pyrimidinyl	H	4-hydroxy
	193.	2-pyrimidinyl	H	4-hydroxy
25	194.	6-pyrimidinyl	H	4-hydroxy
	195.	4-pyridazinyl	H	4-hydroxy
	196.	5-pyridazinyl	H	4-hydroxy
	197.	4-indolyl	H	4-hydroxy
	198.	5-isoindolyl	H	3-amino
30	199.	5-naphthyridinyl	H	3-amino
	200.	6-quinozalinyl	H	3-amino

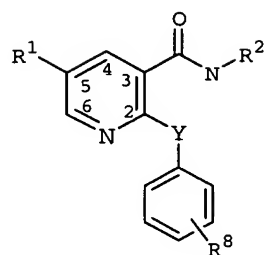
Table 2 (cont.)



5	#	R ²	R ¹	R ⁸
	201.	6-isoquinolyl	H	3-amino
	202.	4-naphthyridinyl	H	3-amino
	203.	5-quinozaliny	H	3-amino
	204.	4-naphthyridinyl	H	3-amino
10	205.	6-indazolyl	H	3-hydroxymethyl
	206.	6-isoindolyl	H	3-hydroxymethyl
	207.	5-indazolyl	H	3-hydroxymethyl
	208.	5-isoindolyl	H	3-hydroxymethyl
	209.	6-benzothienyl	H	3-hydroxymethyl
15	210.	6-benzofuryl	H	3-hydroxymethyl
	211.	5-benzothienyl	H	3-hydroxymethyl
	212.	5-benzofuryl	H	3-hydroxymethyl
	213.	2-benzimidazolyl	H	3-hydroxymethyl
	214.	2-benzoxazolyl	H	3-hydroxymethyl
20	215.	2-benzthiazolyl	H	3-hydroxymethyl
	216.	6-benzimidazolyl	H	3-hydroxymethyl
	217.	6-benzoxazolyl	H	3-hydroxymethyl
	218.	6-benzthiazolyl	H	4-amino
	219.	2-quinazolinyl	H	4-hydroxymethyl

25

Table 3



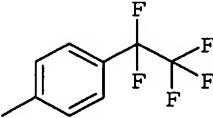
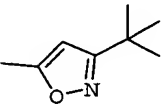
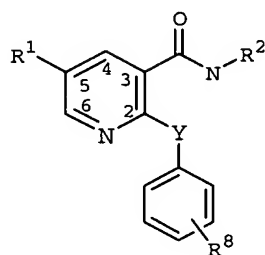
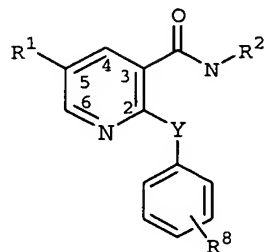
5	#	R^8	Y	R^2	R^1
	220.	4-F	-NHSO ₂ -	4-chlorophenyl	H
	221.	4-F	-NHSO ₂ -	4-chlorophenyl	5-Br
	222.	3,4-diF	-NHSO ₂ -	3-chlorophenyl	H
10	223.	4-Cl	-NHSO ₂ -	3-chlorophenyl	5-Br
	224.	H	-NHSO ₂ -	4-phenoxyphenyl	H
	225.	4-F	-NHSO ₂ -	4-biphenyl	H
	226.	4-F	-NHSO ₂ -	3-isoquinolyl	H
	227.	3,4-diF	-NHSO ₂ -	3-isoquinolyl	5-Br
15	228.	H	-NHSO ₂ -	4-chlorophenyl	H
	229.	4-F	-NHSO ₂ -	4-chlorophenyl	5-Br
	230.	4-F	-NHSO ₂ -	3-chlorophenyl	H
	231.	3,4-diF	-NHSO ₂ -	3-chlorophenyl	5-Br
	232.	H	-NHSO ₂ -	4-phenoxyphenyl	H
20	233.	4-F	-NHSO ₂ -	4-biphenyl	H
	234.	4-F	-NHSO ₂ -	3-isoquinolyl	H
	235.	3,4-diF	-NHSO ₂ -	3-isoquinolyl	5-Br
	236.	H	-NHCH ₂ -		H
	237.	4-F	-NHCH ₂ -		H

Table 3 (cont.)



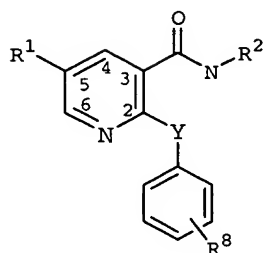
5	#	R ⁸	Y	R ²	R ¹
	238.	4-F	-NHCH ₂ -		H
	239.	4-F	-NHCH ₂ -		H
	240.	4-F	-NHCH ₂ -	3-CF ₃ -phenyl	F
	241.	4-F	-NHCH ₂ -		H
10	242.	4-F	-NHCH ₂ -		H
	243.	3,4-diF	-NHCH ₂ -		H
	244.	H	-NHCH ₂ -		H
	245.	4-F	-NHCH ₂ -		H

Table 3 (cont.)



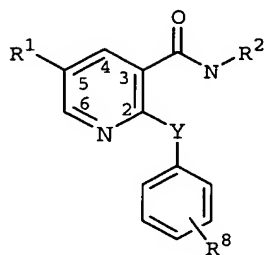
5	#	R ⁸	Y	R ²	R ¹
	246.	4-F	-NHCH ₂ -		H
	247.	4-F	-NHCH ₂ -		H
	248.	3,4-diF	-NHCH ₂ -		H
	249.	H	-NHCH ₂ -		H
10	250.	4-F	-NHCH ₂ -		H
	251.	4-F	-NHCH ₂ -		H
	252.	3,4-diF	-NHCH ₂ -		H
	253.	H	-NHCH ₂ -		H
	254.	4-F	-NHCH ₂ -		H

Table 3 (cont.)



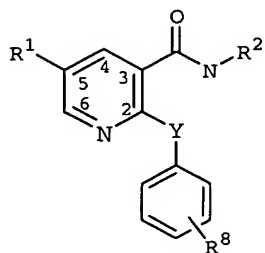
5	#	R^8	Y	R^2	R^1
	255.	4-F	-NHCH ₂ -		H
	256.	4-F	-NHCH ₂ -		H
	257.	3,4-diF	-NHCH ₂ -		H
	258.	H	-NHCH ₂ -		H
10	259.	4-F	-NHCH ₂ -		H
	260.	4-F	-NHCH ₂ -		H
	261.	3,4-diF	-NH(CH ₂) ₂ -		H
	262.	H	-NH(CH ₂) ₂ -		H

Table 3 (cont.)



5	#	R ⁸	Y	R ²	R ¹
	263.	4-F	-NH(CH ₂) ₂ -		H
	264.	4-F	-NH(CH ₂) ₂ -		H
	265.	3,4-diF	-NHCH ₂ -		H
	266.	H	-NHCH ₂ -		H
10	267.	4-F	-NHCH ₂ -		H
	268.	4-F	-NHCH ₂ -		H

Table 3 (cont.)



5	#	R ⁸	Y	R ²	R ¹
	269.	4-F	-NHCH ₂ -		H
	270.	4-F	-NHCH ₂ -		H
	271.	4-F	-NHCH ₂ -		H
	272.	4-F	-NHCH ₂ -		H

Although the pharmacological properties of the compounds of Formulas I-IV vary with structural change, in general, activity possessed by compounds of Formulas I-IV may be demonstrated *in vivo*. The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological *in vitro* assays. The exemplified pharmacological assays which follow have been carried out with the compounds according to the invention and their salts. Compounds of the present invention showed inhibition of KDR kinase at doses less than 50 μM .

BIOLOGICAL EVALUATION

HUVEC Proliferation Assay

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Human Umbilical Vein Endothelial cells are purchased from Clonetics, Inc., as cryopreserved cells harvested from a pool of donors. These cells, at passage 1, are thawed and expanded in EBM-2 complete medium, until passage 2 or 3. The cells are trypsinized, washed in DMEM + 10% FBS + antibiotics, and spun at 1000 rpm for 10 min. Prior to centrifugation of the cells, a small amount is collected for a cell count. After centrifugation, the medium is discarded, and the cells are resuspended in the appropriate volume of DMEM + 10% FBS + antibiotics to achieve a concentration of 3×10^5 cells/mL. Another cell count is performed to confirm the cell concentration. The cells are diluted to 3×10^4 cells/mL in DMEM + 10% FBS + antibiotics, and 100 μL of cells are added to a 96-well plate. The cells are incubated at 37 °C for 22 h.

Prior to the completion of the incubation period, compound dilutions are prepared. Five-point, five-fold serial dilutions are prepared in DMSO, at concentrations 400-fold greater than the final concentrations desired. 2.5 μL of each compound dilution are diluted further in a total

of 1 mL DMEM + 10% FBS + antibiotics (400x dilution).
Medium containing 0.25% DMSO is also prepared for the 0 μ M
compound sample. At the 22-hour timepoint, the medium is
removed from the cells, and 100 μ L of each compound dilution
5 is added. The cells are incubated at 37°C for 2-3 h.

During the compound pre-incubation period, the growth
factors are diluted to the appropriate concentrations.
Solutions of DMEM + 10% FBS + antibiotics, containing either
VEGF or bFGF at the following concentrations: 50, 10, 2,
10 0.4, 0.08, and 0 ng/mL are prepared. For the compound-
treated cells, solutions of VEGF at 550 ng/mL or bFGF at 220
ng/mL for 50 ng/mL or 20 ng/mL final concentrations,
respectively, are prepared since 10 μ L of each will be added
to the cells (110 μ L final volume). At the appropriate time
15 after adding the compounds, the growth factors are added.
VEGF is added to one set of plates, while bFGF is added to
another set of plates. For the growth factor control
curves, the media on wells B4-G6 of plates 1 and 2 are
replaced with media containing VEGF or bFGF at the varying
20 concentrations (50 - 0 ng/mL). The cells are incubated at
37°C for an additional 72 h.

At the completion of the 72 h incubation period, the
medium is removed, and the cells are washed twice with PBS.
After the second wash with PBS, the plates are tapped gently
25 to remove excess PBS, and the cells are placed at -70 °C for
at least 30 min. The cells are thawed and analyzed using
the CyQuant fluorescent dye (Molecular Probes C-7026),
following the manufacturer's recommendations. The plates
are read on a Victor/Wallac 1420 workstation at 485 nm/530
30 nm (excitation/emission). Raw data are collected and
analyzed using a 4-parameter fit equation in XLFit. IC₅₀
values are then determined.

The compounds of examples 16-17 20-21, 25-27, 29, 34-
35, 39-42, 45-46, 52, 54-57, 58-65, 212, 215 and 243-245

inhibited VEGF-stimulated HUVEC proliferation at a level below 50 nM.

Angiogenesis Model

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To determine the effects of the present compounds on angiogenesis *in vivo*, selective compounds are tested in the rat corneal neovascularization micropocket model or the angiogenesis assay of Passaniti, Lab. Invest., 67:519-528 (1992).

10

Rat Corneal Neovascularization Micropocket Model

In Life Aspects: Female Sprague Dawley rats weighing approximately 250 g were randomized into one of five treatment groups. Pretreatment with the vehicle or compound was administered orally, 24 h prior to surgery and continued once a day for seven additional days. On the day of surgery, the rats were temporarily anesthetized in an Isofluorane gas chamber (delivering 2.5 L/min oxygen + 5% Isofluorane). An othoscope was then placed inside the mouth of the animal to visualize the vocal cords. A tip-blunted wire was advanced in between the vocal cords and used as a guide for the placement of an endotracheal Teflon tube (Small Parts Inc. TFE-standard Wall R-SWTT-18). A volume-controlled ventilator (Harvard Apparatus, Inc. Model 683) was connected to the endotracheal tube to deliver a mixture of oxygen and 3% Isofluorane. Upon achieving deep anesthesia, the whiskers were cut short and the eye areas and eyes gently washed with Betadine soap and rinsed with sterile saline. The corneas were irrigated with one to two drops of Proparacaine HCl ophthalmic topical anesthetic solution (0.5%) (Bausch and Lomb Pharmaceuticals, Tampa FL). The rat was then positioned under the dissecting microscope and the corneal surface brought into focus. A vertical

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incision was made on the midline of the cornea using a diamond blade knife. A pocket was created by using fine scissors to separate the connective tissue layers of the stroma, tunneling towards the limbus of the eye. The distance between the apex of the pocket and the limbus was approximately 1.5 mm. After the pocket had been made, the soaked nitrocellulose disk filter (Gelman Sciences, Ann Arbor MI.) was inserted under the lip of the pocket. This surgical procedure was performed on both eyes. rHu-bFGF soaked disks were placed into the right eye, and the rHu-VEGF soaked disks were placed into the left eye. Vehicle soaked disks were placed in both eyes. The disk was pushed into position at the desired distance from the limbal vessels. Ophthalmic antibiotic ointment was applied to the eye to prevent drying and infection. After seven days, the rats were euthanized by CO₂ asphyxiation, and the eyes enucleated. The retinal hemisphere of the eye was windowed to facilitate fixation, and the eye placed into formalin overnight.

Post Mortem Aspects: After twenty-four hours in fixative, the corneal region of interest was dissected out from the eye, using fine forceps and a razorblade. The retinal hemisphere was trimmed off and the lens extracted and discarded. The corneal dome was bisected and the superfluous cornea trimmed off. The iris, conjunctiva and associated limbal glands were then carefully teased away. Final cuts were made to generate a square 3x3mm containing the disk, the limbus, and the entire zone of neovascularization.

Gross Image Recording: The corneal specimens were digitally photographed using a Sony CatsEye DKC5000 camera (A.G. Heinz, Irvine CA) mounted on a Nikon SMZ-U stereo microscope (A.G. Heinz). The corneas were submerged in distilled water and photographed via trans-illumination at

approximately 5.0 diameters magnification.

Image analysis: Numerical endpoints were generated using digital micrographs collected from the whole mount corneas after trimming and were used for image analysis on the Metamorph image analysis system (Universal Imaging Corporation, West Chester PA). Three measurements were taken: Disk placement distance from the limbus, number of vessels intersecting a 2.0mm perpendicular line at the midpoint of the disk placement distance, and percent blood vessel area of the diffusion determined by thresholding.

General Formulations:

0.1% BSA in PBS vehicle: 0.025 g of BSA was added to 25.0 ml of sterile 1X phosphate buffered saline, gently shaken until fully dissolved, and filtered at 0.2 μ m. Individual 1.0 mL samples were aliquoted into 25 single use vials, and stored at -20 °C until use. For the rHu-bFGF disks, a vial of this 0.1% BSA solution was allowed to thaw at RT. Once thawed, 10 μ L of a 100 mM stock solution of DTT was added to the 1 mL BSA vial to yield a final concentration of 1 mM DTT in 0.1% BSA.

rHu-VEGF Dilutions:

Prior to the disk implant surgery, 23.8 μ l of the 0.1% BSA vehicle above was added to a 10 μ g rHu-VEGF lyophilized vial yielding a final concentration of 10 μ M.

rHu-bFGF: Stock concentration of 180 ng/ μ l:

R&D rHu- bFGF: Added 139 μ L of the appropriate vehicle above to the 25 μ g vial lyophilized vial. 13.3 μ L of the [180 ng/ μ L] stock vial and added 26.6 μ L of vehicle to yield a final concentration of 3.75 μ M concentration.

Nitro-cellulose disk preparation: The tip of a 20-gauge needle was cut off square and beveled with emery paper to create a punch. This tip was then used to cut out \approx 0.5 mm diameter disks from a nitrocellulose filter paper sheet (Gelman Sciences). Prepared disks were then placed into

Eppendorf microfuge tubes containing solutions of either 0.1% BSA in PBS vehicle, 10 μ M rHu-VEGF (R&D Systems, Minneapolis, MN), or 3.75 μ M rHu-bFGF (R&D Systems, Minneapolis, MN) and allowed to soak for 45-60 min before
5 use. Each nitrocellulose filter disk absorbs approximately 0.1 μ L of solution.

In the rat micropocket assay, compounds of the present invention will inhibit angiogenesis at a dose of less than 50 mg/kg/day.

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Tumor model

A431 cells (ATCC) are expanded in culture, harvested and injected subcutaneously into 5-8 week old female nude
15 mice (CD1 nu/nu, Charles River Labs) (n = 5-15). Subsequent administration of compound by oral gavage (10 - 200 mpk/dose) begins anywhere from day 0 to day 29 post tumor cell challenge and generally continues either once or twice a day for the duration of the experiment. Progression of
20 tumor growth is followed by three dimensional caliper measurements and recorded as a function of time. Initial statistical analysis is done by repeated measures analysis of variance (RMANOVA), followed by Scheffe post hoc testing for multiple comparisons. Vehicle alone (Ora-Plus, pH 2.0)
25 is the negative control. Compounds of the present invention are active at doses less than 150 mpk.

Rat Adjuvant Arthritis Model:

30 The rat adjuvant arthritis model (Pearson, Proc. Soc. Exp. Biol. 91, 95-101 (1956)) is used to test the anti-arthritic activity of compounds of the Formula I-III, or salts thereof. Adjuvant Arthritis can be treated using two different dosing schedules: either (i) starting time of

immunization with adjuvant (prophylactic dosing); or from day 15 when the arthritic response is already established (therapeutic dosing). Preferably a therapeutic dosing schedule is used.

5

Rat Carrageenan-induced Analgesia Test

The rat carrageenan analgesia test was performed with materials, reagents and procedures essentially as described by Hargreaves, et al., (Pain, 32:77 (1988)). Male Sprague-Dawley rats were treated as previously described for the Carrageenan Foot Pad Edema test. Three hours after the injection of the carrageenan, the rats were placed in a special plexiglass container with a transparent floor having a high intensity lamp as a radiant heat source, positionable under the floor. After an initial twenty minute period, thermal stimulation was begun on either the injected foot or on the contralateral uninjected foot. A photoelectric cell turned off the lamp and timer when light was interrupted by paw withdrawal. The time until the rat withdraws its foot was then measured. The withdrawal latency in seconds was determined for the control and drug-treated groups, and percent inhibition of the hyperalgesic foot withdrawal determined.

25

Formulations

Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of Formulas I-III in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form

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of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and compositions of the present invention may, for example, be administered orally, mucosally, topically, 5 rectally, pulmonarily such as by inhalation spray, or parentally including intravascularly, intravenously, intraperitoneally, subcutaneously, intramuscularly intrasternally and infusion techniques, in dosage unit formulations containing conventional pharmaceutically 10 acceptable carriers, adjuvants, and vehicles.

The pharmaceutically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, including humans and other 15 mammals.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit 20 containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. For example, these may contain an amount of active ingredient from about 1 to 2000 mg, preferably from about 1 to 500 mg. A suitable daily dose for a human or other mammal may vary 25 widely depending on the condition of the patient and other factors, but, once again, can be determined using routine methods.

The amount of compounds which are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on 30 a variety of factors, including the age, weight, sex and medical condition of the subject, the type of disease, the severity of the disease, the route and frequency of administration, and the particular compound employed. Thus,

the dosage regimen may vary widely, but can be determined routinely using standard methods. A daily dose of about 0.01 to 500 mg/kg body weight, preferably between about 0.1 and about 50 mg/kg body weight, may be appropriate. The
5 daily dose can be administered in one to four doses per day.

For therapeutic purposes, the active compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of
10 administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids,
15 gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl
20 cellulose.

In the case of psoriasis and other skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

25 Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin (e.g., liniments, lotions, ointments, creams, or pastes) and drops suitable for administration to the eye, ear, or nose. A suitable
30 topical dose of active ingredient of a compound of the invention is 0.1 mg to 150 mg administered one to four, preferably one or two times daily. For topical administration, the active ingredient may comprise from 0.001% to 10% w/w, e.g., from 1% to 2% by weight of the

formulation, although it may comprise as much as 10% w/w, but preferably not more than 5% w/w, and more preferably from 0.1% to 1% of the formulation.

When formulated in an ointment, the active ingredients
5 may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as
10 propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such
15 dermal penetration enhancers include DMSO and related analogs.

The compounds of this invention can also be administered by a transdermal device. Preferably transdermal administration will be accomplished using a patch either of
20 the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the
25 active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may
30 be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a

lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, sodium lauryl sulfate, glyceryl distearate alone or with a wax, or other materials well known in the art.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The active ingredients are preferably present in such

formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules using one or more of the carriers or diluents mentioned for use in the formulations for oral administration or by using other suitable dispersing or wetting agents and suspending agents. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water, or with cyclodextrin (ie. Captisol), cosolvent solubilization (ie. propylene glycol) or micellar solubilization (ie. Tween 80).

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

For pulmonary administration, the pharmaceutical composition may be administered in the form of an aerosol or with an inhaler including dry powder aerosol.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable non-irritating excipient such as cocoa butter and polyethylene glycols that are solid at ordinary temperatures but liquid
5 at the rectal temperature and will therefore melt in the rectum and release the drug.

The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants,
10 such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. Tablets and pills can additionally be prepared with enteric coatings. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents.

15 The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended
20 claims.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the
25 invention to adapt it to various usages and conditions.

All mentioned references, patents, applications and publications, are hereby incorporated by reference in their entirety, as if here written.